THE HUMAN CEREBROSPINAL FLUID

An Investigation by The Association for Research in Nervous and Mental Diseases

THE HUMAN CEREBROSPINAL FLUID

ASSOCIATION FOR RESEARCH IN NERVOUS & MENTAL DISEASE

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THE HUMAN CEREBROSPINAL FLUID

PAUL B. HOEBER, INC

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THE HUMAN CEREBROSPINAL FLUID

An Investigation of the Most Recent Advances, as Reported by The Association for Research in Nervous & Mental Disease

THE PROCEEDINGS OF THE ASSOCIATION;
NEW YORK, DECEMBER 29TH & 30TH, 1924

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PREFACE

THIS volume represents the fourth publication of the Association for Research in Nervous and Mental Disease. In general, its typographical and editorial treatment conforms to the already established ideas of presentation and publication which have characterized the preceding volumes of the Association.

The articles constituting this volume are here published in extenso, many of them having been presented before the Association in much abbreviated form. The exigencies of financial limitations have in some instances necessitated the elimination of certain tabulations, but wherever this has been done, the tables have been represented by satisfactory summaries.

The questions and answers following the presentation of each paper have been freely edited by those responsible for them, in order that discrepancies and equivocations arising in the course of the discussion should not persist in the permanent, written transcript.

The editorial committee wishes to take this opportunity again of expressing its sincere gratitude to those who labored so conscientiously and successfully to make this volume a complete and comprehensive survey of the human cerebrospinal fluid. The editorial committee feels that this volume represents the most up-to-date publication on this subject, that it comprises material which up to now has been available only in the current periodicals, and that the volume in reality is a symposium representing the latest investigative results and the most current interpretation of both the physiological and the pathological aspects of the human cerebrospinal fluid.

The editorial board wishes to express its deep sense of obligation to the *Archives of Neurology and Psychiatry; Surgery, Gynecology and Obstetrics* and the *Archives of Otolaryngology*, for the generous loan of cuts and blocks, which has materially reduced the cost of publication. It also desires to acknowledge the services of the publishers, Paul B. Hoeber, Inc., and their staff in the preparation of this volume.

The clinical contributions which appear in this volume are based upon over five thousand recorded examinations of the human cerebrospinal fluid obtained from all conceivable pathological states, and represent almost all known clinical conditions.

The section of the book concerned with the normal characteristics of the human cerebrospinal fluid has been included in order that this book may not only be a record of present-day research and investigation, but also that it may be of value as a standard reference volume.

The material presented before the Association for Research in Nervous and Mental Disease two years ago on the subject of epilepsy still awaits further investigation and addition before it will appear as a separate volume. It is hoped that a further attack upon this most serious problem may be made in the near future in order that this effort may take its place in proper sequence with the other publications of this Association.

The officers of the Association through this medium wish to thank the members of the Association for their interest and their attendance which have served to make each one of its yearly meetings an occasion of intense scientific interest and of great personal pleasure and satisfaction to all the members of the Association.

H. A. R.
T. K. D.

New York,
May, 1926.

SECTION I

THE NORMAL HUMAN CEREBROSPINAL FLUID

Section I

THE NORMAL HUMAN CEREBROSPINAL FLUID

Chapter I

PRESIDENTIAL ADDRESS

Historical Résumé of the Knowledge of the Human Cerebrospinal Fluid

WALTER TIMME, M.D.

OUR historical record in regard to the cerebrospinal fluid begins, as do most things medical, with the Greeks. We know that they must have been aware of accumulations of fluid in the brain in disease states such as hydrocephalus, for they tapped the brain in these cases. Craniotomy was also performed, we know not how early, among the semi-civilized peoples of the Americas, also, presumably, for hydrocephalus. Whether or not the Greeks believed that the mucus which came from the posterior nasopharyngeal space was a fluid exuded from the brain we do not know, but they called it after the pituitary gland, apparently believing that it took its origin from that structure. But more than this has not come down to us. Herophilus evidently knew of the existence of the ventricles and of the chorioid plexus, but he does not mention the fluid contained in the ventricles. Erasistratus (grandson of Aristotle?) describes the ventricles of the brain but omits reference to the fluid contained within them. Galen describes an excretion, watery in character, emanating from the brain and collecting in the ventricles, whence it was forced into the nasal cavity through the ethmoid bone, via the infundibular process of the pituitary gland. Many of the Greeks, of course, in their search for the seat of the soul, hesitated at the ventricles; but their search was for the spirit and not for water, and thus the fluid probably escaped them.

The next stepping-stone is, of course, as usual, Vesalius. He also knew the ventricles as well as the chorioid plexus, and while, indeed, he mentions a watery humor of the brain, it is in a quite casual way, and probably he gave little or no weight to its importance or distribution. Vesalius, in the sixteenth century, was probably the first to recognize the fact that the normal content of the ventricles is not air but fluid, but went little further.

It is not until we reach the end of the eighteenth century that we find investigators who recognized the presence of a fluid in the brain and cord, even though its nature or purpose was unknown to them.

The credit of having recognized the cerebrospinal fluid as a real, possibly circulating medium must be divided among Valsalva, Sömmering, Cotugno and Baron Albertus Haller of Göttingen, investigators of the eighteenth century.

Cotugno, to whom the discovery is usually allotted, found the fluid in fish and in some amphibia, but is said not to have detected it in man. This may seem curious until it is understood that occasionally in some fish the fluid is not really fluid, but a gummy, gelatinous mass, which might readily have been recognized as important where a fluid was not. Valsalva is credited with having detected the fluid in cutting into the cord of a dog and associating it with the fluid of the synovial membranes. Sömmering believed the fluid in the cavities of the brain to be organized, to be the common source of the nerves of the brain and body generally, and that it was really the "organ of the soul." He cited the Scriptures, "and the Spirit of God moved upon the face of the waters," as indicating the correctness of his view. Goethe, Kant and the eighteenth century philosophers ridiculed him for this attitude.

Albertus Haller, professor at Göttingen, in his "Physiology," which was printed in several editions beginning in 1747, in the 1764 and in the 1766 Edinburgh editions of the work describes the cerebrospinal fluid as follows:

"The vapour which is secreted into the ventricles of the brain of a healthy person is in like proportion absorbed again by the inhaling veins: or if any part abounds, that it descends through the bottom of the ventricles to the basis of the skull, and from thence into the loose cavity of the spinal medulla. That this is the case appears from the watery tumours in the lower part of the spinal medulla following in those who have an hydrocephalus."

And again: "This cavity, of which there is one in each hemisphere of the brain, is called its anterior ventricle; and it is naturally filled with a vapour, which is frequently condensed into water or jelly."

As for the cord: "Between the arachnoides and the dura mater there exhales a vapour, which is frequently condensed into a reddish water and produces a true dropsy."

But in his conclusions he believes the nervous fluid to be the instrument of sense and motion and to consist of elastic and electrical matter, "as the moderns will have it."

It took another half century to develop the idea of the protective character of the cerebrospinal fluid, and we are indebted to François Magendie for this advance. He recognized not only that the space between the piarachnoid and the medulla is much larger than is necessary to contain the organ, and that this space is filled up with a serous liquid, but that this liquid is under some pressure, for when the membrane is punctured it spurts out many inches in height. "It is easy to see," says Magendie, "how efficacious must be the protection derived from this liquid which similarly surrounds the spinal marrow." Luschka and Naunyn followed Magendie with anatomical and physical discussions of the fluid. In 1842, Lange's "Anatomy" gave much space to an exclusive discussion of the cerebrospinal fluid. Theory and speculation then arose as to its origin, its distribution, its circulation: Was it an exudate, a transudate, or a secretion? Originally it was obtained for study through a trephine opening in the skull, but, as this was a tedious and somewhat dangerous method, other means for obtaining it were sought. Corning, in 1885, introduced a needle into the intravertebral cavity for the purpose of cocainizing the cord in certain spinal affections. This is the first record we have of spinal puncture. He entered at one of the lower dorsal levels, but, unfortunately, left no record of his technique.

A few years later, Wynter, of London, drained the cerebrospinal fluid in a case of tuberculous meningitis. He made a skin incision at the level of the second lumbar vertebra, somewhat lateral to the spine, and introduced a trocar and cannula through the wound. By manipulation of the trocar downward and towards the median line, he finally entered the canal. He drained the fluid in this case continuously through a slender rubber cannula, with much improvement in the immediate symptoms of the disease. This technique was followed in several cases of tuberculous men-

ingitis, with temporary improvement in all, although the final results of the disease were fatal.

This leads us directly to the nice technique of Quincke for spinal puncture, perfected by him during the decade preceding 1891. It necessitated no skin incision and needed no trocar and cannula; moreover, it was applied at a much safer level for the integrity of the cord. He used a plain, strong needle only and entered the spinal canal between the fourth and fifth lumbar vertebrae. Several cases of hydrocephalus were thus treated by Quincke, with much relief in the symptoms, and he concluded that spinal puncture for therapeutic purposes was indicated in cases of intracerebral pressure. Quincke measured the pressure of the fluid and examined it chemically and physically, although more or less crudely. Lichtheim, following Quincke, applied his technique with success to many meningitic conditions. Following the publication of the results obtained by these men, many punctures were done in America, as well as in Europe, with varying therapeutic results, until at the present time lumbar puncture is more or less a routine procedure for both diagnostic and therapeutic purposes. The chemical, bacteriological and physical examinations have been more and more perfected; differences of pressures at varying levels, with their diagnostic import, have been studied; punctures at critical levels, such as the cisterna-magna puncture of Ayer, have added largely to our means for diagnosis and therapeusis; and, lastly, the introduction of foreign substances, such as lipiodol, into the cord in order to facilitate *x*-ray examination, as practised by Sicard in Paris, has brought this chapter in neurological medicine to the present date.

Chapter II

THE EMBRYOGENESIS OF THE HUMAN CEREBROSPINAL FLUID

Its Sources, Circulatory Pathways and Destination, Together with Its Relation to the Blood and Lymph Vascular Systems

WALTER HUGHSON, B.S., M.D.

KNOWLEDGE of the probable source and circulatory pathways of the human cerebrospinal fluid has become available only in comparatively recent years, although Magendie published his observations on the character of the fluid just a century ago. The difficulties of studying its physiological and anatomical properties are such that even now many of the problems involved seem almost impossible of solution. There can be little wonder, therefore, that during the seventy-five years following Magendie's observations, the advances made in the knowledge of the cerebrospinal fluid were more or less desultory and in no sense gave positive data in regard to its general properties and relationship. Even today so fundamental a fact as the origin of the fluid has yet to be proved absolutely, and though a mass of data lends almost incontrovertible support to the chorioid plexus theory, this cannot yet be accepted as a demonstrated scientific fact.

During the past ten years, Weed, in a splendid series of papers, has cleared up finally many perplexing points in what might be called the life history of this body fluid. In any such study as the present one, frequent reference must be made to his many contributions; and, indeed, much has been taken almost bodily from his articles. His observations during this period of time have proceeded in a methodical manner from the earliest development of the cerebrospinal meninges and first appearance of the contained fluid, to an exhaustive research into the ultimate destination of this fluid in the adult animal. Already, clinical application of his studies has shown that the facts advanced for experimental

animals are entirely analogous to conditions found in the human being.

In probably no other part of the body is physiological control in support of anatomical knowledge so necessary as in a study of the cerebrospinal fluid and its pathways. This fact is further emphasized by the wide discrepancy in interpretation of similar facts made by various authors; and as a result only those facts can be accepted as final which are supported by experimental evidence of the highest possible quality. Fortunately, the technique of experimental analysis has admitted of uniform results in the hands of certain investigators.

The Source of the Cerebrospinal Fluid

To speak of the embryogenesis of a fluid, the adult origin of which still lies somewhat in doubt, is hardly a logical procedure; but a brief review of the facts at hand in regard to the activity of the chorioid plexus will probably furnish the necessary justification.

Faivre first described the glandular structure of the chorioid plexus, and this fact, supported by Luschka's observations a short time afterward, marked the abandonment of the earlier theory that the cerebrospinal fluid was elaborated by the leptomeninges. The hypothesis advanced at that time, that the chorioid plexus elaborates the greater portion of the cerebrospinal fluid, has formed the working basis of all subsequent investigations.

With the development of histological and cytological technique, much has been done to correlate the well-established presence of intracellular secretion granules in the cells of the plexus and the actual production of the liquid surrounding the cells. Other authors, notably Cappelletti, Pettit, Girard and Meek, using a combination of pharmacological and histological methods, demonstrated increased secretory activity under the influence of muscarine, pilocarpine, etc., while atropine and hyoscyamine diminished it. On histological examination, following the use of these drugs, definite changes in the character of the cells of the plexus were found.

Clinical evidence has also furnished strong support to the general hypothesis. Experimental and pathological obstructive internal hydrocephalus points definitely toward an intraventricular elaboration of the fluid. Strong support is lent to the general theory by Cushing's observation of an exudation of clear fluid from a

chorioid plexus exposed in the course of an exploration; by Weed's catheterization of the aqueduct of Sylvius, resulting in a sustained flow of fluid; and, finally, by Dandy's extirpation of the chorioid plexus in an obstructed lateral cerebral ventricle, thus preventing the development of an internal hydrocephalus. Weed's studies on the development of the cerebrospinal spaces, which will be reviewed in some detail, add another link to the chain. This same author has advanced further evidence indicating that possibly the perivascular spaces and even the ependymal cells lining the ventricles may elaborate a certain amount of fluid into the subarachnoid spaces, where this fluid mixes with the liquid produced in the cerebral ventricles. This fact may possibly account for the known difference in character between the ventricular and spinal fluids.

The Formation of the Perineural Spaces

His and Kölliker were the first to demonstrate in man the development of all the meninges from mesenchyma and also the differentiation of the cerebrospinal membranes to form the subarachnoid space. Reford, working in Mall's laboratory, made the only attempt previous to Weed's to solve the problem of development of the cerebrospinal space by the method of injection. Unfortunately, Reford's work was never published. Methods of injection of the subarachnoid space in the adult have, in general, always involved the introduction of the foreign solution under considerable pressure. Such a method in the embryo is obviously impractical, as the injection of a true solution under pressure would surely cause a diffusion through the delicate embryonic membranes and the injection of a suspension would also result in inaccuracy, due to probable rupture at some point of the containing arachnoid. Weed, fully conscious of these facts and indeed insisting on their recognition, made all his observations by the introduction of fluids at normal pressure, or, more correctly stated, by the replacement of the embryonic cerebrospinal fluid with some foreign solution. In addition, Weed insisted that the injection should be made with a true solution, isotonic with the blood and cerebrospinal fluid, rather than with emulsions or suspensions of carbon granules.

Weed's replacement experiments were all carried out on embryo pigs, because in the pig the central nervous system and its coverings develop in a manner quite analogous to the central nervous system of the human being. The technique of these experiments

was extremely ingenious, the fluid being introduced through the caudal central canal and withdrawn from one or the other lateral ventricles. Following the injection these embryos were kept alive in the incubator for varying periods of time, usually one hour, thus allowing the spread to become complete. The solution injected consisted of a one per cent concentration of potassium ferrocyanide and iron-ammonium citrate. Precipitation of Prussian blue granules in situ was then effected by fixation with formalin and a small amount of hydrochloric acid. The investigation was carried out with the idea of correlating the physiological spread of the embryonic cerebrospinal fluid with the gradual transformation of the perimedullary mesenchyma into the three fully formed meninges and incidentally the concomitant development of the chorioid plexus.

In brief, the results of Weed's experiments were as follows: By careful syringe injection through the central canal of the spinal cord of a living pig embryo of 9 mm., the ventricles can be fairly well filled without rupture of any element. The solution then spreads to the bulbar region and extends outward into the large fourth ventricle. At this stage the solution is wholly contained within the medullary canal system, there being no evidence whatever of spread outwards from either the third or fourth ventricle. At the 13 mm. stage, using the replacement method of injection, with the exception of an area of condensation of the fluid on the anterior half of the ventricular roof, there is no difference from the stage preceding, and there is still no indication of a meningeal fluid cushion corresponding to the adult subarachnoid space. From the 14 mm. stage onward, however, the picture gradually changes. In a pig embryo of 14.5 mm., there is, for the first time, indication of a spread through the roof of the fourth ventricle. Here, there is a delicate, fusiform extension of the fluid caudalward from the roof of the fourth ventricle, lying between this point and the skin. At this same stage is first noticed on the roof of the ventricle the small depression which marks the beginning of formation of the chorioid plexuses. At 18 mm., conditions are much the same, but there is exhibited a new phenomenon: The chorioid plexus invagination has now divided the roof into two parts, and from these two parts has taken place the entire escape of the injection fluid into the pericerebral tissues. The spread of the fluid is considerably greater than at the last stage, extension taking place in all directions; that is, superiorly, inferiorly and

laterally. There is still no evidence of a perispinal spread. Further spread now takes place rapidly, with increase in size of the embryo, and at 21 mm. the fluid can be traced caudalward in the perispinal spaces to the point of injection. In the cephalic region the spread is very extensive. The rhombencephalon is completely surrounded, and laterally the Prussian blue is shown as a dense mass in intimate relation to the cranial nerves where they join the brain stem. The spread, therefore, is now almost complete, the only areas not entirely surrounded being the anterior mesencephalon and the cerebral hemispheres. Study of a 26 mm. embryo shows the injection occupying the whole medullary canal system and also completely surrounding the cerebrospinal axis. In addition, there is an extension of the granular material laterally along each spinal nerve, extending only so far, however, as the ganglia on the posterior roots. The adult relationship holds, therefore, at the 26 mm. stage, so far as the pathway of the periaxial spaces, the distribution of the cerebrospinal fluid and the sole communication between the ventricles and the perispinal spaces are concerned, this last fact being at variance with the findings of Bichat and Mierzejewsky, but in accordance with the observations of Dandy and Blackfan.

Weed explains this spread largely on the basis of filtration, the fluid going from a point of higher to one of lower pressure. There must, however, be some mechanism whereby passage outward of the normal protein content of the cerebrospinal fluid may take place. This phenomenon may be effected either by a phagocytic property of the cells of the area membranacea of Weed, or else by a process similar to but slower than the normal fluid passage. In replacement experiments where suspensions of India ink were used, neither of these factors could be demonstrated, due doubtless to the size of the carbon granules.

The Relationships of the Cerebrospinal Fluid and the Subarachnoid Space

With this brief and necessarily incomplete review of the development of the subarachnoid space, indicating periods in its apparent functional activity, we may turn to the problem of ascertaining the relationship between the developing chorioid plexuses and the extension of fluid into the periaxial spaces. Weed again has investigated this problem, using pig embryos for his experimental observations. In the 14 mm. stage, we have already learned that

there is a beginning passage of the ventricular fluid into the periaxial spaces. This extraventricular extension occurs practically simultaneously with the first indication, in the pig embryo, of the chorioid plexuses of the fourth ventricle. It would surely seem, therefore, that the time of appearance of the chorioid plexuses in relation to the spread of the fluid must offer some evidence in regard to the first elaboration of fluid by these structures. In the 18 mm. stage the chorioid plexus is well advanced, and at 20 mm. the tufts in the fourth ventricle are quite marked; but not until the 19 mm. stage is there any indication of the plexus in the third and fourth ventricles. A perfectly definite differentiation occurs at 23 mm., a fact suggestive of some relationship to the complete periaxial spread found in embryos of this length. With this gradual development of plexuses and the coincident passage of fluid into the pericerebral and periaxial spaces, it seems reasonable to conclude that with the first appearance of the chorioid plexuses a more rapid production of cerebrospinal fluid occurs, necessitating the passage of fluid into the periaxial spaces and lending further support to Weed's suggestion in regard to the movement of fluid from a point of higher to one of lower pressure.

The Cerebrospinal Fluid Circulation

Although no evidence was brought forward by Weed to elucidate the interesting problem of the development of the various foramina, in all his experiments histological examination showed that the membranes were intact throughout and that the spread took place through the differentiated areae membranaceae, superior and inferior; nevertheless, in a consideration of the adult circulation of the fluid, we are obliged to accept the existence of the foramina of Luschka and Magendie. The exact mode of escape, however, is still a matter of uncertainty. Whether these foramina are artefacts or whether there develops an actual functioning opening in the velum, it is through these three foramina, or at least from the region of the tela chorioidea, if through an intact membrane, that the fluid produced in the ventricles passes into the subarachnoid space.

The route of flow of the fluid formed in the lateral ventricles, therefore, is through the foramen of Monro into the third ventricle, by the aqueduct of Sylvius into the fourth ventricle and thence through the foramina into the subarachnoid space. From the cisternal dilatation of the subarachnoid space in the region of

the medial cerebellobulbar angle, the fluid gradually seeps downward in the spinal subarachnoid space, but passes with much greater rapidity about the base of the brain, completely around the hypophysis cerebri in the sella turcica, as demonstrated by the author, and thence more slowly over the hemispheres. This movement is probably facilitated by impulses transmitted to it by the vascular system. In the spinal region there is a similar circulation of fluid upward. The speed of flow of this cerebrospinal fluid is governed largely by the density of the delicate, mesh-like trabeculae extending from the outer continuous arachnoid membrane to the pia mater, with which they merge. The arachnoid, trabeculae and pia mater are all covered by flattened, polygonal mesothelial cells. In addition, all the blood vessels and nerves crossing the subarachnoid space are also covered by these same mesothelial elements. The meshes referred to above vary in size from fine reticular spaces over the cerebral hemispheres to broader channels in the cerebral sulci and about the spinal cord, reaching their greatest capacity in the cisternal dilatations about the cerebellobulbar angle. Obviously, therefore, the flow of cerebrospinal fluid is obstructed but little in the wide channels; while in the regions of the smaller meshes the flow is definitely retarded.

At this point it might be well to call attention to the relation of these mesothelial cells to the subarachnoid and perivascular spaces, for there is a distinct fluid-containing space about each of the perforating vessels. The cells of the pia mater turn inward to form the outer wall of such a perivascular channel, while the cells of the arachnoid, covering the vessel as it traverses the subarachnoid space, form the inner wall. Thus each blood vessel penetrating the nervous system is surrounded by a cell-enclosed, periadventitial fluid channel, which communicates directly with the subarachnoid space. This perivascular fluid channel, where the mesothelial-cell cuff ceases, continues inward to connect directly with perineuronal spaces about the nerve cells. These ultimate fluid spaces are only potential in character, but represent an important accessory fluid system of the cerebrospinal axis, affording a direct pathway between nerve cell and subarachnoid space.

In speaking of a potential space the probable explanation is that under normal pressure conditions the circulation in these spaces is inactive. In order to demonstrate the assumed patency of these spaces, it must be possible either to force fluid into these

regions by a markedly increased pressure, or else to have it drawn in by some influence within the central nervous system. This latter method, if possible, is greatly to be preferred and fortunately is at once available, having been made use of in the great majority of circulation and absorption experiments. Weed and McKibben first showed that the normal cerebrospinal fluid pressure in animals could be markedly reduced by the intravenous injection of strongly hypertonic solutions of sodium chloride. This reduction in pressure resulted not only from an actual withdrawal of fluid from the arachnoid space, but also from a shrinking of the brain itself. In a later experimental study, Weed used this method to demonstrate not only the possible circulatory pathways but also the routes of absorption of the fluid. A solution of potassium ferrocyanide and iron-ammonium citrate was here again used as the replacement fluid and the precipitation of the Prussian blue in situ demonstrated graphically the anatomical pathways described above. This procedure was also used by the author to prove the existence of a continuation of the subarachncid space about the hypophysis cerebri.

The Destination of the Cerebrospinal Fluid

Probably the most important factor concerned in the life history of the cerebrospinal fluid, certainly from a clinical standpoint, is the ultimate destination and distribution of this fluid, and by this we mean, of course, absorption. It would be difficult to enumerate fully the number of conditions which exhibit symptoms referable to an increased intracranial pressure. This increase is probably in most cases due to a hypersecretion and a diminished absorption, the degree of either one or the other varying with the particular disease.

The literature regarding the absorption of the cerebrospinal fluid is very extensive, and time does not permit here of a comprehensive review. It will be enough to mention some of the leading theories advanced and to state the present status of the problem. Key and Retzius were the first to study the problem and their monograph still stands unique in the skill of its preparation and splendid character of its plates. They found the chief pathway of absorption to be by way of the Pacchionian granulations into the great dural venous sinuses and, in addition, an accessory drainage indirectly into the lymphatic system. When the supposed

discovery was made that the Pacchionian granulations were absent in higher animals and in infants, various authors regarded the views of Key and Retzius as inadequate and attempted to explain the process on other bases. Mott first suggested the possible passage of fluid through the perivascular channels into the cerebral capillaries in animals upon whom ligation of the carotid or vertebral arteries had been done. Dandy and Blackfan felt that absorption was a diffuse process from the entire subarachnoid space and that the cranial portion was more efficient than the spinal, while Cushing suggested a valve-like mechanism for drainage into the venous sinuses. The Pacchionian granulations have since been shown by Weed to be present in all ages of every species.

Weed's investigation of the question of cerebrospinal fluid absorption is most convincing in character and has the great advantage of being carefully controlled both from an anatomical and physiological viewpoint. The first step in the investigation was to effect replacement of the cerebrospinal fluid with a foreign injection solution without in any way changing the normal relationship of the intracranial arterial and venous pressures and the cerebrospinal fluid pressure. These normal pressures and their relationship have been established by Weed and Hughson. Two types of injection were made: a suspension of carbon granules and a true solution of foreign salts. In the second type of experiment these injection solutions were introduced when the cerebrospinal fluid pressure had been reduced to a point well below zero, and the injection fluid then maintained at a level never in excess of the established normal for the particular experimental animal. At the end of each experiment the animals were killed and immediately injected through the heart with formalin, and, where the ferrocyanide-citrate mixture had been used, with sufficient hydrochloric acid to precipitate the Prussian blue. These granules remain unaltered by the technique of histological preparation.

Without going into too great detail, Weed showed the following facts: In the replacement experiments the precipitation of the Prussian blue was wholly localized within the subarachnoid space and the nervous tissue was absolutely free from coloration, these facts being shown both grossly and microscopically. There was also no penetration of the perivascular spaces. The granules, however, were traced directly into the arachnoidal villi, projecting into the basilar dural sinuses, particularly the cavernous sinuses. Furthermore, the granules could be seen passing through the meso-

thelial cells, capping the villus and through the endothelial cells of all the dural sinuses.

However, where the hypertonic sodium chloride solution was used, as in the second type of experiment, a very different picture was observed. Here the absorption could be traced through the meninges and cerebral substance for a distance of 1 to 5 mm.; the perivascular channels and the ependymal lining of the ventricles also showing the injection granules. Nañagas had already shown absorption through the ependymal lining of the ventricles in cases of experimental obstructive hydrocephalus, but neither he nor Weed was able to confirm Foley's observation that a process of resorption took place in the cells of the chorioid plexus, a view held by certain European investigators. The author has shown a further pathway of absorption; namely, into the substance of the hypophysis. In experiments similar to the above, granules could be traced into the stroma of the pars buccalis, outlining in many instances the cellular columns of this portion of the gland. This fact suggests a possible intimate relation between the cerebrospinal fluid, blood stream and hypophysis at this point. Clinical support of these observations is afforded by the work of Aycock and Amoss on local specific therapy in poliomyelitis.

With this weight of evidence at hand, the view of various foreign authors that the fluid passes into the cerebral substance through the interstices between the ependymal cells and between the cells of the subependymal spaces (von Monakow) is hardly tenable; nor is the frequent reference made to the lymph vessels and spaces of the brain and meninges and their relation to the lymphatic glands borne out by experimental evidence (Stern, Dahlström).

Possible criticism of the pathways established by the use of intravenous injections of hypertonic sodium chloride cannot as yet be met by definite experimental data; that is, so far as the normal use of these channels is concerned. That marked changes in cerebrospinal fluid pressure occur in various pathological states is, of course, a matter of common knowledge, and it is most reasonable to believe that under conditions of increased pressure these accessory means of absorption may function actively and serve in much the manner of the complementary space of the thoracic cavities. Furthermore, there is some evidence to indicate a fluctuation of the normal chloride content of the blood during and following digestion, which could readily effect slight changes in the

cerebrospinal fluid pressure. Cushing and Foley have shown this to be true by the reduction of pressures following ingestion of sodium chloride in considerable quantities, and the author has called attention to the relief of intracranial hypertensive headache following the ingestion of this salt. Furthermore, we have every reason to believe that very slight changes in the normal blood concentration may have some physiological effect on the system in general.

The Relationship between the Vascular System and the Cerebrospinal Fluid

In this connection the passage of substances from the bloodstream into the central nervous system and cerebrospinal fluid might be taken up with advantage. Unfortunately, few data of a convincing nature are available, although clinically the matter is one of the greatest importance. Stern and Gautier, among others, have investigated the passage of various substances from the blood stream into the central nervous system and subarachnoid space. They regard the chorioid plexus as an apparatus of filtration and purification: a protecting glandular membrane. They have sought in the cerebrospinal fluid, after injection into the general circulation, volatile substances such as alcohol, acetone, chloroform, etc., and fixed substances as bromides, iodides, strychnine, lithium, lead, arsenic and mercury, and various coloring matters, such as pigments and acids from the bile and glandular products. These authors have found certain substances circulating and fixed in the central nervous system and others absent, the amounts varying considerably with the different substances used. They are unable to explain these results by any chemical or physical law, but apply to this supposed selective mechanism the name "hemato-encephalic barrier." Discussion of this problem must be purely speculative. Unless the drug used is one with an especial affinity for the nervous system, such as strychnine, there is immediately presented the problem of the passage of a substance in solution from a point of lower to one of higher pressure. This particular phase of the problem has been given consideration in the intravenous administration of antiluetic drugs after the cerebrospinal fluid pressure has been reduced by the administration of hypertonic sodium chloride solutions. Many interesting problems await further investigation in this particular field.

The pressure of the cerebrospinal fluid and its relation to the blood vascular system is another problem of the greatest impor-

tance and one which has occupied the attention of many observers. The reported results have shown great discrepancies, and in consequence, frequent repetitions of the experimental methods have been undertaken in recent years. To quote a few reported records: Leonard Hill believed that normal pressures in experimental animals might vary from 0 to 50 mm. of mercury; Dixon and Halliburton, 40 to 70 mm. Ringer's solution; Becht, 112 mm. normal salt solution; Foley and Putnam, 127 mm. normal salt solution; and more recently Weed and Hughson have reported an average of 119 mm. Ringer's solution. In one of Weed and Hughson's typical experiments under ether anesthesia, fluctuations in pressure over a two-hour period of observation were but 11 mm. It is safe to say, therefore, that these later observations are more correct, and that marked fluctuations in pressure during the experimental period may be regarded as an index of improper technical control. Accepting the Monro-Kellie doctrine, which has been subjected to experimental proof by Weed and Hughson, the following hypothesis, as stated by Weed and McKibben, affords an extremely satisfactory working basis for experimental observations: "the cranial cavity is relatively fixed in volume and is completely filled by brain, cerebrospinal fluid and blood; variations in any one of these three elements may occur, compensation being afforded by alteration in the volume of one or both of the remaining elements."

Leonard Hill believed that intracranial venous pressure and intracranial pressure were identical, and this view was held generally until Dixon and Halliburton demonstrated "independent changes in pressure occurring as the result of the secretory activity"; but they believed that intracranial venous pressure was higher than that of the cerebrospinal fluid. Becht confirmed this view of independence of pressure, while indicating an inconstant relation between venous and cerebrospinal fluid pressures. All of these observers took their readings of venous pressure by trephining posteriorly into the torcular Herophili. This method is subject to many experimental defects, as indicated by the wide divergence of the pressure readings. Using a much simpler method for recording intracranial venous pressure, Weed and Hughson were able to show that in practically every case the cerebrospinal fluid pressure was definitely above (5 to 50 mm.) that of the sagittal sinus; while they agreed with Dixon and Halliburton and Becht that alterations in intracranial venous pressure caused

alterations in the cerebrospinal fluid in the same direction, but of lesser magnitude, and that the reverse condition also held true. This pressure relation doubtless plays a large part in the passage of fluid from the subarachnoid space into the dural sinuses and in addition affords a ready explanation of Wegefarth's experiments. This author showed that an experimental communication between subarachnoid space and superior sagittal sinus remained patent without hemorrhage into the meningeal cavities for at least four days. Removal of cerebrospinal fluid in these animals, however, resulted in immediate intrameningeal hemorrhage. This could only be possible if the fluid pressure were greater than that in the sinuses.

Weed and Hughson brought further evidence to bear on the independence of this fluid pressure by studying intracranial venous and arterial pressures when the cerebrospinal fluid pressure had been reduced to below zero by intravenous injections of hypertonic sodium chloride solutions. Except for a momentary change in the arterial and venous levels during the period of injection, these pressures are thereafter practically unaffected, while the cerebrospinal fluid pressure falls to its extreme low level and gradually returns to normal after the blood has regained its proper tonicity.

Referring to Reford's work, Sabin, in 1914, made the following statement: "The arachnoid space has as definite a form as the coelom and it never connects with the lymphatics." This conclusion is in marked contrast to that held by various European investigators. Von Monakow speaks of "the lymph vessels of the meninges," indicating thereby a direct intracranial connection with the lymph glandular apparatus. Stern, although recognizing the fact that the great majority of anatomists deny the existence in the nervous tissues of the cerebrospinal axis of channelled vessels analogous to the lymphatics, nevertheless seems to place considerable emphasis on the subarachnoid communication with the peripheral lymphatic system by the lymphatic slits of the spinal nerves (described by Finel and Nageotte).

Injection experiments by practically all investigators have shown the presence of the injection mass in the lymph glandular system. Key and Retzius, Quincke, Leonard Hill, Ziegler, Spina, Cushing, Dandy and Blackfan, to mention a few of them, all speak of this fact, but in almost every instance the appearance of the dyes used in the lymphatics is considerably delayed: from one-half to one hour after the injection has been made. This immediately

raises the point as to whether this appearance in the lymphatics is due to any direct connection, or simply an indirect route through the blood stream. Weed, however, states that "it seems fair to assume that the absorption of the cerebrospinal fluid is a twofold process, being chiefly a rapid drainage into the great dural sinuses and in small part a slow indirect escape into the true lymphatic vessels."

Discussion

The following questions submitted to Dr. Hughson before the Commission, together with the answers to them, are here reported verbatim.

Dr. Barker: Has Dr. Hughson any ideas about the outlook for experimentally diminishing (temporarily) the resistance of the barrier between the blood and the spinal fluid for therapeutic purposes? For instance, might it be possible to injure the barrier a little so as to facilitate the entrance of substances from the blood (i.e., intravenous injections of antitoxins or chemical substances)?

Dr. Hughson: Some work that we have been doing recently has shown that with various toxic products in the blood there is a reduction in cerebrospinal fluid pressure. Whether the reduction is due to a decreased secretion or an increase in the rapidity of absorption, which, if true, would indicate some lowering of resistance at that point, is the only supposition I know of that would be suggestive in this relation.

Dr. Tilney: Will Dr. Hughson state a little more in detail the histological character of the connection which he thinks exists between the subarachnoid space and the glandular portion of the hypophysis?

Dr. Hughson: By the intravenous injection method of reducing cerebrospinal fluid pressure (which produces a suction around the hypophysis), and also by using increased pressure of injection, we were able to demonstrate that the subarachnoid space was continuous around the entire gland. The space undoubtedly is not open in the presence of normal pressure, but by this induced suction or by increased injection pressure, the injection mass could be traced entirely around the hypophysis and indeed could be made out easily in the cells of the arachnoid and pia by microscopical examination. The injection fluid used was potassium ferrocyanide and iron ammonium citrate. The Prussian blue granules were found in the cells of the pars buccalis, having passed through the arachnoid just as they do in every other part of the central nervous system. They were also found to a lesser extent in the pars nervosa of the hypophysis. I do not know anything about the passage of substances in the opposite direction, but it is reasonable to suppose that if they go one way, they can go the other.

Dr. Pollock: Does the absence of substances in the spinal fluid indicate their non-existence in the central nervous tissue after intravenous injection?

Dr. Hughson: No, not necessarily. These substances which, for instance, were injected intravenously were found in the central nervous system in varying quantities, in addition to being in the cerebrospinal fluid.

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Chapter III

THE NORMAL HUMAN CEREBROSPINAL FLUID: REVIEW OF THE LITERATURE

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OBSERVATIONS on the normal cerebrospinal fluid, that is, in cases showing no clinical signs of cerebrospinal fluid disorder, have accumulated in considerable number. However, the vast majority of studies of the cerebrospinal fluid are made in the presence of disease and much of our knowledge of the normal cerebrospinal fluid is derived by comparison of the properties of the fluid found in various diseased states and deductions therefrom, and from animal experimentation.

History

The anatomists of ancient times, doubtless, observed the cerebrospinal fluid, but its importance did not strike their attention. At least, there is no record of any observations on its presence until the time of Galen. Herophilus mentions the ventricles and the chorioid plexus but not the fluid. Erasistratus of Julis (330–250 B.C.) describes four cavities in the brain but does not mention the fluid. Galen (131–201 A.D.) does not mention the fluid in the spine or cisterns. He expressed himself only concerning the fluid in the ventricles which he viewed as a conveyor of animal spirits and as an "excremential liquid, expressed from all parts of the brain into the ventricles particularly the fourth, where it is collected and removed by way of the ethmoid bones and the infundibulum." Vesalius regarded the ventricular fluid as a lubricant. Vidus-Vidius (d. 1569) noted it and considered it a post-mortem product. Varolius (1543–1575) attributed to the chorioid plexus the property of pumping fluid into the ventricles.

Willis (1695) refers to the ancient view of the cerebrospinal fluid as the purveyor of animal spirits, but speaks of the modern view; that the ventricular water is concerned with carrying out waste products from the brain. He offers no better means of escape for it than the ancients' view; namely, by way of the infundibulum and the cribriform plate.

Vieussens (1641–1716) found an aqueous humor in the ventricles, produced by the pituitary, pineal and chorioid glands—a vehicle for animal spirits contributed by the blood. He believed these "acqueous juices of the brain" were prevented by the valve bearing his name from getting into the subtentorial region. This he believed he had proved by ventricular injection experiments.

Stalpartius Vander Weil (1727) refers to a clear watery fluid escaping from the ear in a case of head injury.

Robert Whytt (1764) attributed tuberculous meningitis to a serous exudate and denominated acute hydrocephalus "dropsy of the brain."

Albertus de Haller (1766) was thoroughly familiar with the fluid in the ventricles and discussed it at length but failed to detect its true significance.

Cotugno receives credit for discovering the cerebrospinal fluid or at least its importance, although Bilanchoni states that Valsalva had previously found "an ounce of a certain liquid in cutting the cord membrane of a dog, a liquid resembling that seen in articulations." In his "Memoir de Ischiade Nervosa," in 1764, Domenico Cotugno calls attention to the space within the spine not filled by the cord, in which is, in man, in health, "un vapeur sale," and in an infant dying during birth, "un vapeur sanguinolente." He asks, "Pourquoi ces collects aqueuses ont-elles enchappé aux anatomistes?" And he answers, by saying that when they examine the brain they first separate the head from the trunk and the liquid escapes and air fills the spaces. He believed the water in the ventricles and around the spinal cord identical. He states that the quantity was four or five ounces in man, and demonstrated its presence in living fish and a large sea turtle but could not find it constantly in dogs or birds.

The modern conception of the cerebrospinal fluid began with Magendie's contributions to the *Journal de Physiologie Expérimentale*, January 10, 1825. His observations were accurate and truly remarkable in view of the chaotic state of knowledge on the subject at the time. His pupil, Jodin, appends to Magendie's monograph of 1842, a review of the literature to that time. He summarizes Magendie's views:

"L'eau existe chez l'homme sain. Elle n'est plus bornée aux ventricles. C'est un liquid qui existe dans les cavités, et enveloppe de toutes parts l'organe cérébro-spinal. Le liquide ventriculaire communique librement avec celui de la superficie; cette communication a lieu par une ouverture constante chez l'homme. Ce liquide n'est plus l'excrément, le vehicula de l'esprit animal; c'est en réalité le moyen que la nature emploie pour maintenir toujours pleine une cavité qui, avec des parois inflexibles, renferme un organe variable dans ses dimensions."

Following Magendie's brilliant observation, Luschka and Ecklar studied the anatomy of the subarachnoid region, Cavazzani studied the physiology, Naunyn studied the pressure of the crebrospinal fluid; Carl Schmidt (1850) expressed the view that the cerebrospinal fluid was more than a transudate. Faivre (1853) regarded it as a secretion.

The present-day conceptions of the meningeal spaces, and much information concerning their fluid content, date from the publication of the brilliant monograph by Key and Retzius (1876). Their experiments, however, on physiology gave rise to the belief that the Pacchionian bodies were the means of escape of the cerebrospinal fluid and that by them it was drained into the great sinus. These bodies are probably pathological granulations and not the physiological portals of exit which these writers supposed.

Corning (1855) discovered spinal anesthesia by injecting a cocaine solution into the eleventh dorsal interspace.

Wynter (1891) drained 4 cases of tuberculous meningitis with a trocar through the second lumbar interspace after incising the skin. Morton (1891) duplicated the procedure of Wynter.

It was left to Quincke (1891) to simplify and perfect the procedure of lumbar puncture. That step has been the means of making this procedure of universal clinical value. Without incision he passed a plain needle through the skin and a lumbar interspace into the subarachnoid space. He regarded it, at that time, as a therapeutic measure.

Lichtheim (1893) suggested the possibility of using lumbar puncture as a diagnostic procedure. Browning (1894) reported a number of spinal punctures. Fuheninger (1895) performed and reported 107 lumbar punctures. Jacoby (1895) reported 30 lumbar punctures. Thereafter, lumbar puncture became an accepted procedure, and marked the beginning of more exact knowledge of the cerebrospinal fluid in health and disease.

Physical Properties

The normal human cerebrospinal fluid is a transparent, colorless fluid of crystalline clarity, in which no sediment forms on standing.

Quantity

Neither the exact nor average quantity of cerebrospinal fluid in man has been determined. It probably varies with the individual. Cotugno's (1770) early estimations were probably not far from the truth. He gave 125 to 156 c.c. as the amount in man. Magendie (1825) reckoned the amount of cerebrospinal fluid as 62 to 372 c.c.; he gave 62 c.c. as the average amount, of which 20 to 30 c.c. are found in the ventricles.

Nearly all authors are in agreement with Mott (1910), who declared that the quantity of human cerebrospinal fluid in normal conditions in the adult varies from 100 to 150 c.c.

Freezing Point

Levi (1902)	−.59°c.
Sollmann (1903)	−.535°c.
Fuchs and Rosenthal (1904)	−.53°c.
Pende	−.59°c.
Quincke	−.56.°c. to −.75°c.
Mott (1910)	−.51°c. to −.56°c.
Polányi (1911)	−.566°c. to −.678°c.
Mestrezat (1912)	−.57°c. to −.59°c.
Levinson (1919)	−.56°c. to −.58°c.
Depisch and Richter-Quittner (1922)	−.56°c. to −.60°c.

Specific Gravity

Halliburton	1.007 to 1.008
Kafka	1.002 to 1.008
Zdarek	1.007
Polányi	1.005 to 1.007
Mestrezat	1.00759 (20 normal specimens at 15°c.)
Nawratzki	1.0073 to 1.008 (same for the horse)
Levinson	1.0064 to 1.007
Pende	1.007–1.010
Borelli and Datta	1.007–1.009
Williamson	1.005–1.009
Hammarstein	1.007–1.008
Levinson	1.0064–1.007

Viscosity

Soda (1921), investigating the viscosity of the cerebrospinal fluid, usually found it apt to be increased when the protein concentration was high. Alkalinity and the number of cells influenced viscosity, but to a lesser extent.

Viscosity Compared with Water as Unity

Borelli and Datta (1906)	1.059–1.049
Galletta (1908)	1.008–1.024
Levy Valeusi (1911)	1.000–1.105
Polányi (1911)	1.020–1.027 at 38°c.
Levinson (1919)	1.0424–1.0489

Conductivity

Polányi (hydrocephalic fluid), 0.01136, 0.01280, 0.01527 and 0.01452 at 20°c. Formula: $\frac{1}{\text{ohm} \times \text{Cm.}}$.

Levinson (non-meningitic fluid), 0.01513, 0.01365, 0.01513 at 25°c.

Surface Tension

Polányi, 7.35, 7.15, 7.16, 7.20 dynes at 20°c.

Location

The cerebrospinal fluid is to be found in the ventricles of the brain and in the subarachnoid space of the brain and spinal cord. It lies also in the perineural subarachnoid space surrounding the cranial nerves; i.e., beneath the epineurilemma. Worthy of special mention are the following facts: The subarachnoid space surrounds the entire inner ear, cochlea, utricle, saccule and canals,

also the olfactory nerve and bulb as far as the cribriform plate (Weed). It surrounds the optic nerve to the globe of the eye, where it lies in the episcleral space within the capsule of Tenon (Schwalbe, Albert and Schnitzler). It extends down the vagus to the middle of the neck or episternal notch. It surrounds the hypoglossus almost to the base of the tongue. It covers the spinal accessory for a distance of two centimeters below the base of the skull (Weed). The other cranial nerves are similarly surrounded within the skull. All parts of the subarachnoid space contain cerebrospinal fluid and may be regarded as diverticuli of the subarachnoid of the base of the brain. Finally, the subarachnoid space extends outward for a short distance along the anterior and posterior roots of the spinal nerves (Sicard and Cestan).

Source

It is now generally accepted that the chorioid plexus is the source of most of the cerebrospinal fluid. The debate as to whether the chorioid plexus is merely a dialyzing membrane, as Mestrezat believed, or a filter or an ultra-filter, as Halliburton stated, or a glandular structure of highly selective activity capable of being stimulated to increased activity by various drugs (Weed, Dixon and Halliburton, and Pettit and Girard) still goes on.

Willis (1664) called attention to the glandular appearance of the "reddish granulations" in the ventricles.

Faivre (1854) described vacuoles in the cells in histological sections of the chorioid plexus.

Luschka (1885) affirmed the secretory nature of the cell activity of the chorioid plexus.

Kingsbury (1897) described globules in the chorioid epithelium in certain fishes.

Findlay (1899) demonstrated these intra-cyto-plasmic globules by histological section and staining in man, and interpreted this as the formation of cerebrospinal fluid.

Galeotti (1897) watched globules pass out of the cells of the chorioid plexus in swallows and rabbits and observed the cells form again after the collapse.

Pettit and Girard (1902) observed the formation and extrusion of globules from the cytoplasm of the cells of the chorioid plexus by opening the ventricle of laboratory animals and observing the chorioid plexus, under the microscope, while bathed in the cerebrospinal fluid.

Pettit and Girard were not willing to accept the activity observed as unaltered physiology because the globules become increasingly numerous the longer the living tissue was observed, instead of diminishing, as would be expected in such an artificial arrangement; and because the globules are more numerous in histological sections the slower the fixation of the tissue.

These authors, however, proceeded to prove the secretory activity of the chorioid plexus experimentally. They observed characteristic glandular response following the administration of ether, urea, atropine, muscarine and theobromine.

Cavazzani (1899) studied the effect of the injection of lymphagogues of Heidenhain, e.g., peptone, extract of eel's blood, glucose, chloride and iodide of sodium; and although in some instances the rate of flow was increased, the amount of ash was not increased.

Cappelletti (1900) stimulated a greatly increased flow of cerebrospinal fluid in dogs with ether and pilocarpine, and caused a diminution of flow with atropine and hyoscyamine. Amyl nitrite had no effect.

As to the derivation of the cerebrospinal fluid, Mott (1910) says, "The composition of the fluid is against it being a transudation from the blood or a lymphatic secretion, and the following facts prove this conclusion: (1) It contains 0.02 per cent of proteins against 7 per cent in blood plasma; (2) it contains 0.02 per cent of proteins against 4.5 per cent in body lymph; (3) there is an absence of lipochrome; (4) there are no leucocytes in the normal fluid; (5) in enteric fever there is absence of agglutinins; (6) it has no haemolytic action on the blood corpuscles of other animals; (7) it contains no alexins."

Dandy (1919) very ingeniously proved the chorioid plexus the source of the cerebrospinal fluid in the ventricles. He blocked the foramen of Monro on one side of a dog's brain, and removed the chorioid plexus of the opposite ventricle, sparing the ependyma, and then blocked the foramen of Monro on that side.

The ventricle on the former side became greatly distended with fluid, while the ventricle on the latter side collapsed. The ependyma as a source of cerebrospinal fluid was thus also eliminated.

The secretory action of the chorioid plexus is highly selective. It permits the passage, from the blood into the cerebrospinal fluid, of acetone and urea, alcohol, chloroform and hexamethylena-

mine. In a certain number of cases, arsenic has been recovered in the lumbar fluid after arsenical intravenous treatment of syphilis of the central nervous system.

For the most part dyes, drugs and other substances introduced intravenously or hypodermically are denied entrance to the cerebrospinal fluid. Tetanus toxin injected subcutaneously is excluded. Agglutinin in typhoid fever is absent.

On the other hand, foreign substances introduced into the subarachnoid space are readily ejected, particularly normal saline and crystalloids, but colloids not so rapidly (Mott, Witte, Crowe, Dixon and Halliburton).

Lees and Barlow state, "We may here add that cerebrospinal fluid as obtained from any point below the fourth ventricle cannot be an absolutely pure secretion; it must contain waste products resulting from cerebral metabolism; for into the subarachnoid space surrounding the brain open the lymphatic sheaths of all the cerebral arteries, and Dr. Bevan Lewis has shown that the nerve cells of the brain are placed within pericellular sacs, each of which has a definite lymphatic connection with the wall of a small blood-vessel."

Additional contributions of fluid come from the canalicular system surrounding the cells and vessels of the brain, which is in direct communication with the subarachnoid spaces described by Mott.

Perivascular, pericapillary, perineuronal and pericellular spaces have been demonstrated in the brain in continuity with the subarachnoid spaces (Robin, His, Mestrezat, Weed, Mott). The perivascular and perineuronal spaces are unlined. The pericellular spaces present neuroglial elements in their walls. These spaces contribute a small part of the cerebrospinal fluid. This secretion contains the waste products of nerve cell activity and is in a sense the lymph of the central nervous tissue (Spina, Lewandowsky, Weed).

The flow of the accessory supply of cerebrospinal fluid is from the pericellular spaces along the perivascular spaces to the subarachnoid spaces, and not the reverse, as viewed by Mott. It is improbable that absorption occurs into the capillaries and vessels. But the blood stream carries nutriment to the nerve cell, and the pericellular spaces receive, and the perineuronal and the perivascular spaces carry away the waste products. That is the functional arrangement of blood supply and lymphatic drainage elsewhere

in the body, and the central nervous system has no other lymphatic system (Weed).

Several authors, Loeper, Askanazy and Hassin, suggest that the chorioid cells have an absorptive function. Possibly these cells pick out harmful products of nervous metabolism in order to render them more absorbable.

Meek (1907) injected pilocarpine and muscarine, and found that the chorioidal cells became larger during secretion, and that their cytoplasm was differentiated into a clear outer and an inner granular zone. This is the reverse of other secreting cells; for example, the alveolar cells of the parotid, which become smaller during activity and in which the cytoplasmic differentiation is also reversed.

Bard (1917) estimated that the surface area of the chorioid plexus is about one square meter. He reasons that it is legitimate to assume that the cuboidal cells of so large a surface may play the part of a dialyzing membrane quite adequate for a constant supply of cerebrospinal fluid, whose rate of formation will be governed by the physical laws of permeability rather than by the factors which govern secretion.

Mestrezat and Ledebt (1921), by dialyzing horse serum through collodion, obtained a fluid of the composition characteristic of the cerebrospinal fluid. By introducing dialyzing sacs into the peritoneal cavity of animals they obtained a colorless, limpid, non-albuminous fluid, "exactly similar" to the cerebrospinal fluid in chemical composition.

Becht and Gunnar (1921), working in the laboratory, concluded that neither adrenalin, pituitrin, pilocarpine nor atropine increases the formation of cerebrospinal fluid. Any increase in flow occurs during the pressor stage of the drug action and is due to the mechanical effect of the intracranial increase in arterial and venous pressure. For when the pressor phase ceases, the fluid forced out of the cerebrospinal chambers returns to them.

Grynfeltt and Euzière (1919) studied the comparative activity of chorioidal and ependymal cells in animals killed by bleeding and by hanging. In animals killed by bleeding the chorioid cells had the appearance of cells in active secretion, presumably for the purpose of maintaining intracranial pressure. Ependymal cells show a similar though less active state. In animals killed by hanging no such state of cellular activity was evident, there being intracranial hypertension.

Circulation

The chief source of the cerebrospinal fluid is the chorioid plexus, lying in the cavity of the ventricular system. The fluid arising in the lateral ventricle flows through the foramina of Monro into the third ventricle, thence through the iter into the fourth ventricle, then through the medianly located foramen of Magendie and the laterally located foramina of Luschka, in the tela chorioidea, into the subarachnoid space of the brain and spinal cord.

The cerebrospinal fluid is constantly renewed from the chorioid plexus. Weed very skilfully passed a catheter through the iter, in dogs, into the third ventricle and got a continuous secretion of fluid.

Schmorl (1910) called attention to the physical and chemical differences in the cerebrospinal fluid in different regions in 10 cases dying with icterus. Seven of them showed colorless ventricular fluid and bile-tinged spinal fluid. In the 3 in which the fluid in the ventricles as well as the spinal fluid contained bile, the chorioid plexus was injured. He also reported 7 cases of paresis, all with a positive Wassermann test in the spinal but only one with a positive test in the ventricular fluid. In 2 cases of scarlet fever, the Wassermann test was positive in the spinal fluid and negative in the ventricular fluid.

Goldmann (1913), after injecting trypan-blue into the lumbar region, found the cord and brain except the cerebral cortex stained.

Golla, using colloidal carbon in the same manner, found the cortex slightly stained after a number of days, though less intensely than the other parts of the nervous system.

Boyd (1914) ventured the following: "From observations on the absorption and excretion of phenolsulphonephthalein injected into the subarachnoid space, it appears probable that the entire quantity of cerebrospinal fluid is completely renewed about every four hours. Granting that the average volume of fluid is somewhere about one hundred or one hundred and twenty cubic centimeters, this would give a total secretion of between six and seven hundred cubic centimeters, in the course of twenty-four hours."

Dandy (1919) substituted India ink for cerebrospinal fluid in the ventricles. Almost immediately the ink filtered into the cisternae. Then the cerebellar subarachnoid space rapidly filled. Gradually filaments of ink spread outward and upward in the

sulci of the hemispheres. It took from forty-five to seventy-five minutes to reach the more remote parts of the longitudinal sinus. Dandy considered that the slow movement toward the longitudinal sinus disproved the belief that the chief escape of cerebrospinal fluid is into that sinus, because phenolsulphonephthalein is absorbed and excreted at the normal rate before the lapse of that length of time.

Cathelin (1921) maintained that there is a circulation of the cerebrospinal fluid comparable to that of the blood and lymph. Secreted by the chorioid plexus, the cerebrospinal fluid, he held, flowed from the ventricles throughout the subarachnoid space and returned to the blood via (1) the spongy tissue of the perivascular spaces, (2) the lymphatics and (3) the thoracic duct, to the left subclavian vein. He based his conclusion as to the escape of the cerebrospinal fluid back to the blood on the dye experiments of Flatau and Sicard.

Weigeldt (1921), after studying 1500 specimens of cerebrospinal fluid, obtained from ventricles, cisternae, and the cervical, dorsal and lumbar regions, found that both normal and pathological fluids show a progressive increase in cells and amount of albumin from the cervical to the lumbar region.

Becher (1921) experimentally showed that while there is no true circulation of the cerebrospinal fluid, it is not at rest. During ventricular systole the pulsation of the brain causes a movement of the fluid toward the caudal end of the subarachnoid space, followed during diastole by a return in the opposite direction. These pulsations give rise to oscillations which after conversion into sine waves are propagated through the spinal fluid at the rate of about three meters per second. The pulsating spinal vessels influence the wave very little. The respiratory waves pass in the same direction. Thus a constant ebb and flow, sufficient to cause a degree of mixing of the subarachnoid contents, is produced.

Solomon, Thompson and Pfeiffer (1922) showed during in vitro experiments that blood serum, when mixed with spinal fluid, seeks the lowest level; and they express the opinion that "we may, therefore, assume that when the blood serum is introduced into the subarachnoid space, it will tend to reach the lowest portion of the cerebrospinal fluid system by a slow diffusion process." They seem to favor the idea that "the movement of the introduced substances (into the spinal fluid) may depend either on circulation of the cerebrospinal fluid or, what is more probable, on a

diffusion of the substances due to osmotic and specific gravity effects." These authors found that neutral phenolsulphonephthalein diffused rapidly through cerebrospinal fluid, whether placed at the bottom or at the top of the column.

Young and Alpers (1924) made the following interesting observations: Swift-Ellis serum introduced into the anterior horn of the lateral ventricles and into the cisterna magna was found in the lumbar spinal fluid after twenty-four hours, as shown both by the gross appearance of the spinal fluid and by evidence of the presence of the serum in an increased cell count and amount of total protein present. It was found, moreover, that the serum introduced in this way could still be detected after forty-eight hours, but had disappeared at the end of seven days. Moreover, serum which had been introduced into the lumbar subarachnoid space was found to have reached the cisterna magna in small quantities at the end of twenty-four hours, but no evidence of its presence in the cisternal fluid could be found after forty-eight hours. In this experiment, also, the serum could be detected grossly in the cisternal fluid at the end of twenty-four hours but could not be detected after forty-eight hours. On the other hand, serum could not be detected in the ventricular fluid either grossly or by the presence of increased cells and protein, twenty-four hours after the injection of Swift-Ellis serum in the lumbar region. These observations would seem to indicate that there is a ready communication between the various loci in the subarachnoid space and that a substance such as serum introduced in the cisternal or ventricular region either diffuses downward rapidly, or is carried down into the lumbar region by a downward flow of spinal fluid, or settles down into the lumbar region because of its greater specific gravity.

It has been amply demonstrated that a neutral dye, phenolsulphonephthalein, introduced into the ventricles, may be recovered in the cisternal and lumbar fluid, and that dye introduced into the lumbar subarachnoid space may be found in the ventricular fluid. The former result occurs much more rapidly, that is, in two to three minutes, than the latter, which takes place in from fifteen to forty-five minutes (Dandy and Blackfan, Dahlström and Wideröe, Stern, Solomon, Thompson and Pfeiffer).

Pulsations

Becher (1922) studied the pulsating waves of the brain and spinal fluid graphically, from tracings on revolving drums. For a full

discussion of this subject, the reader is referred to Becher's original article (see bibliography, page 57).

Absorption

That the cerebrospinal fluid returns to the blood circulation, there can be no doubt. Absorption occurs chiefly into the great sinuses of the dura by way of the arachnoidal villi, passing through the substance of the cells composing the villi and the myxomatous groundwork of the mesodermal lining of the villi (Weed), and not between the cells or into the Pacchionian granulations (Key and Retzius) which are absent in infants (see page 15 for Weed's views).

The greater concentration of colloids and crystalloids in the blood as compared with the cerebrospinal fluid, which is as poor in salts as any body fluid, causes osmosis (Mott). Filtration is also probable, due to the "vis à tergo" caused by steady production of cerebrospinal fluid by the chorioid plexus and consequent elevation of pressure in the cerebrospinal spaces (Weed).

Some absorption of the cerebrospinal fluid occurs from the spinal subarachnoid, probably very little, as indicated by phenolsulphonephthalein experiments of Weed, although Dandy and Blackfan found the rate of absorption from spinal spaces as great as from the cranium. In addition to the major system of drainage, the arachnoidal villi, there is an accessory system, by way of the perineural spaces beneath the epineurolemma of the cranial and spinal nerve. From these it is taken up by the lymphatic vessels adjacent to them, but there is probably no direct lymphatic drainage from the subarachnoid space nor any drainage into veins or capillaries (Weed).

The observation of Kramer, that there is an ascending flow of the cerebrospinal fluid in the central canal of the spinal cord by way of a caudal metapore, has not been confirmed.

Wislocki and Putnam (1921), after producing hydrocephalus in a kitten, showed that absorption occurs to some extent from the ventricles in hydrocephalic animals and that the pathway of escape is through the ependyma into the intercellular spaces and finally into the perivascular spaces. The rate of diffusion of a true solution from the ventricles into the brain substance is fairly rapid; that of a colloidal suspension somewhat slower. There was no evidence of absorption by the chorioid plexus.

Weed (1923), in a series of very skilful experiments, using India ink in some, the Prussian-blue precipitation method in others, aided by intravenous injections of hypertonic salt solutions, observed that "the arachnoid villi are of importance in that they apparently afforded the anatomical pathway for the absorption of the cerebrospinal fluid into the venous system. In the partial injections, the precipitated granules were traced through the core of the basilar villi, through the arachnoid mesothelial cells capping the villus and through the endothelial cells of the dural sinus, directly into the lumen of the great venous channel of the base of the brain. The process appeared to be one of passage of the foreign solution directly through the cytoplasm of the cells as through a cellular membrane. In the completely injected specimens (i.e., those animals in which the experimental replacement was continued for several hours) an identical passage of the fluid, as shown by the precipitated granules, was apparent in the villi about the superior sagittal sinus.

"With the evidence indicating that the foreign solution (and, therefore, the cerebrospinal fluid) was absorbed directly into the dural venous sinuses by way of the arachnoid villi, an attempt was made to discover other areas of vascular absorption. The vessels traversing the subarachnoid space, those beneath the pia and those of the arachnoid membrane were found to be in no way concerned with the process; in every case the fluid was prevented from reaching the vascular channels by the barrier presented by the cells lining the subarachnoid space. No absorption by the ependymal lining of the cerebral ventricle or by the cells of the chorioid plexuses was observed. Likewise no fluid was found to have passed toward the capillary bed of the nervous system by way of the perivascular spaces. Investigation of these and other possible pathways of absorption failed to reveal any escape of the fluid from the subarachnoid space into blood vessels except by way of the arachnoid villi."

Weed concluded that the pathway of absorption of the cerebrospinal fluid into the blood stream under normal conditions is by way of the arachnoidal villi into the great dural venous sinuses. Under the influence of an increased salt content of the blood, effected by the intravenous injection of strongly hypertonic solutions, absorption takes place also by way of the perivascular channels and through the ependymal lining of the cerebral ventricles into the capillary bed of the nervous system. In the normal

process, filtration may be the physical factor of greatest importance, but after the intravenous injection of strongly hypertonic solutions, osmosis and diffusion apparently play the only active rôles.

Pressure

The cerebrospinal fluid is under more than atmospheric pressure. Measured by a manometer through the lumbar puncture needle, the pressure varies with the position of the subject. It is much higher in the sitting position than in the recumbent posture. Extreme flexion of the head increases the pressure, as do also sneezing, coughing, crying, grunting, straining and emotional states; for example, fear or mild shock or fainting will cause a distinct fall in cerebrospinal fluid pressure. Respiration shows a slight rise and fall in pressure. There are pulsations in the spinal fluid, frequently seen by the surgeon.

Leonard Hill (1896), in his studies on cerebral circulation, concluded that the "cerebrospinal fluid preserves its peculiar constitution in normal conditions of pressure only. If it is drawn off, its space is taken by a serous transudation. That the rate of this transudation directly depends on the differences between cerebral venous pressure and the subarachnoid pressure. Diminished subarachnoid pressure produces increased transudation until the cerebral venous pressure and the cerebrospinal fluid pressure are again equalized. That no pathological increase in cerebral tension can be transmitted by the cerebrospinal fluid, because this fluid can never be retained in the meningeal spaces at a tension higher than that of the cerebral veins."

Wegefarth (1914) demonstrated inequalities in the cerebral venous and cerebrospinal fluid pressure, the latter exceeding or being constantly reduced to the former.

Dixon and Halliburton (1914) concluded that the opposite was true.

Becht (1920) determined that the two pressures were almost equal, varying with conditions.

Bard (1917) suggested that the "pineal gland appears to be the organ which regulates the pressure of the cerebrospinal fluid." He hypothesized that it acts as a peripheral sensorial organ of baroscopical perception and as an automatic center of this special function.

Haden (1919) reported diminution in intracranial pressure following intravenous injection of a 25 per cent glucose solution, in cases of meningitis.

Weed and McKibben (1919) found that intravenous hypotonic solutions cause augmentation of the pressure of the cerebrospinal fluid in the cat, and hypertonic solutions cause a fall.

Cushing and Foley (1920) noted the decrease in cerebrospinal fluid pressure following ingestion of hypertonic solutions, and a slow but definite rise in pressure following intraintestinal administration of distilled water.

Foley and Putnam (1920) caused a marked fall in the cerebrospinal fluid pressure in dogs by introducing hypertonic solution both by mouth and by rectum.

Becht and Matill (1920) concluded that "the changes in cerebrospinal fluid pressure corresponded quite closely to the venous changes. While the arterial pressure may have a direct effect on the fluid pressure, the changes in the fluid were for the most part due to the venous changes. The changes in the fluid pressure due to injected tissue extracts were comparable to and dependent on the vascular changes. All those tried produced depressor effects except adrenalin and posterior lobe pituitary extract, which produced pressor effect. There is no indisputable evidence that any of the extracts used has a specific action on the cerebrospinal fluid pressure. Changes produced in the fluid by tissue extracts are mechanical, in so far as the extracts have any vascular effect. Extracts of chorioid plexus have a definite lymphagogue action."

Becht (1920) found that in normal animals intracranial venous and fluid pressures, while positive, are always less than arterial pressure. Venous and fluid pressures are almost, but not exactly, equal; no law can be formulated stating which is under the greater pressure. Venous and fluid pressures vary in the same direction and to some degree proportionally in nearly every case; the pressure may or may not vary in the same direction as the arterial pressure.

Sachs and Malone (1921) observed diminution in brain volume and pressure after intravenous injection of a 30 per cent sodium chloride solution.

Foley (1921), following hypertonic solution administration, demonstrated a reversal of the flow of cerebrospinal fluid. Not only was the dye-bearing fluid in the subarachnoid space carried into the ventricles and taken up by the usual paths of exit, the arachnoidal villi, but it was also found in the perivascular brain

spaces and in the vessels of the chorioid plexus, having passed through the cells of the plexus in a retrograde direction, the action being induced by the increased osmotic value of the blood.

Weed and Hughson (1921) concluded that intravenous injection of Ringer's solution caused a temporary rise in cerebrospinal fluid pressure, distilled water caused a prolonged rise, and that hypertonic solutions caused a prolonged and profound fall preceded by a sharp rise. They also observed the cerebrospinal fluid pressure to be higher than that of the brachial vein, except after the intravenous injection of hypertonic solutions, and that changes in cerebrospinal pressure induced by intravenous injection of solutions of various concentrations seem to be independent of the changes in the systemic and intracranial arterial or venous pressures, and that the pressure of the cerebrospinal fluid, while dependent in part upon cerebral arterial pressure and in larger measure upon cerebral venous pressure, is independent of either. They decided the cerebrospinal fluid pressure was always higher than that in the superior sagittal sinus.

Barré and Schrapf (1921), basing conclusions upon 310 lumbar punctures, decided that the normal maximum of cerebrospinal fluid pressure is 200 mm. of water in the lying posture, and 400 mm. in the sitting posture. They observed that raising the head while in the sitting posture will raise the lumbar pressure from 50 to 100 mm. pressure. But in the lying posture, extension of the neck has no such effect.

These authors concluded that the normal lumbar spinal fluid pressure varies between 150 and 400 mm. in the sitting posture, and between 50 and 200 mm. in the lying posture. They found, also, that the emotional state, the emotional response to the puncture and the vasomotor state influence greatly the cerebrospinal fluid pressure. In a frightened individual showing pallor there may be no flow of cerebrospinal fluid on lumbar puncture and the pressure may be zero. On reassurance and reaction, the pressure will become quite normal. They explain this as a vasoconstrictor phenomenon, and believe that this proves the dependence of the cerebrospinal fluid pressure upon the arterial and venous pressure, intra- and extradural.

Zylberlast-Zand (1921) investigated the cerebrospinal fluid pressure with particular regard to the difference in the lying and sitting postures, and flexion of the head. She found the pressure in healthy adults to vary from 10 to 100 mm. lying, and from 200 to

300 mm. sitting. In the lying posture flexion of the head increased the pressure from 20 to 120 mm. In the sitting posture, flexion of the head caused a fall in pressure up to 50 mm.

Leriche (1922) recognized hypotension of the cerebrospinal fluid as the cause of certain cases of (1) headache, vertigo and nausea, (2) convulsive states, (3) semi-comatose states, and (4) shock with fever and delirium. The cause is either loss of cerebrospinal fluid through lumbar puncture or surgical procedure, or insufficient production by the chorioid plexus, as occurs in shock and fevers or other causes of a drop in arterial pressure. The treatment is hypodermic injection of artificial serum and, where indicated, surgical treatment.

Wertheimer (1922) applied clinically intravenous injections of hypertonic solutions of glucose and hypotonic fluid and distilled water, according to the pressure indication in the cerebrospinal fluid. He treated selected cases suffering with epileptic seizures with fair success.

Bárány (1923) decided that the minimum pressure of the cerebrospinal fluid could be determined by having the patient breathe deeply during lumbar puncture, until the fluid pressure in the manometer would sink no lower. He estimated the average minimum pressure at 40 to 60 mm. in the lying posture.

Foley (1923) demonstrated experimentally that the intravenous administration of 30 per cent sodium chloride solution causes a marked decrease in the subarachnoid spinal fluid pressure, producing a retrograde absorption of fluid in the ventricles, through the chorioid plexus and ependyma. The current of the fluid was completely reversed, a retrograde flow from the subarachnoid space to the ventricles being set up. There was an increased rate of absorption along the sheaths of the cranial and spinal nerves. The reversal of the flow is caused by absorption of the fluid into the capillaries in the brain substance. Absorption directly into the vessels traversing the subarachnoid space also occurs.

Solomon, Pfeiffer and Thompson (1923) called attention to the necessity of a standard method in taking manometric pressure readings during lumbar puncture. They suggested that the reading be taken only after the patient has become emotionally and physically relaxed, waiting several minutes, six to seven, after the insertion of the needle, when the column is at a constant level.

Block and Oppenheimer (1924) found that when cerebrospinal fluid is withdrawn there is a fall in the blood pressure. Usually the

greater the amount of cerebrospinal fluid that is withdrawn by lumbar puncture, the greater the fall in systolic, diastolic and pulse pressures. For every cubic centimeter of cerebrospinal fluid that is withdrawn, there is a fall of a little less than one millimeter of mercury in the spinal fluid pressure. Usually high pressure in the arterial system is associated with high pressure in the cerebrospinal fluid.

The following estimations of the pressure of the cerebrospinal fluid have been recorded. They were all made with the subject lying on his side, which is the posture of choice in making observations in the cerebrospinal fluid by the lumbar procedure. Differences in technique and instruments result in discrepancies in observations. The following figures refer to pressure in millimeters of water:

Cybierski	72 to 90	
Adamkiewitz	80 to 100	
Key and Retzius	160 to 200	
Bergman	80 to 160	
Quincke	40 to 60	
Falkenheim	160 to 200	
Schulzen	52 to 100	
Kronig	125 to 150	
Parisot	100 to 150	
Boveri	170 to 200	
Westregat	60 to 120	
Sicard	200 to 300	
Cottin and Saloz	200 to 300	
Levinson	130 to 140; child, 45 to 90	
Falkenheim and Naunyn	child, 50 to 200 (1st year)	
Quincke	150; child, 40 to 60	
	Sitting	Lying
H. Claude	230 to 250	150
L. Bard	400	200
Fontecilla and Sepulveda		60 to 150
Leicher		135
Parisot		60 to 120

Chemistry

In reporting the chemistry of the cerebrospinal fluid, the older values are so inconsistent and contradictory that only the most recent figures are considered of sufficient accuracy to be recorded here.

MESTREZAT'S ANALYSIS*

	Normal cerebrospinal fluid	Serum, 25 oz. of one man (Schmidt)
Freezing point	−0.57°c.	−0.56°c.
Water	996.67	908.84
Fixed material	10.93	91.16
Organic material	2.13	82.58
Albuminoid material	0.18	
Albumoses and peptones	0.00	0.00
Amino-acids	0.010	0.0099
Urea	0.06	0.10 −0.30
Ammonia	?	0.004–0.010
Reducing materials (glucose)	0.53	1.0 −1.50
Chlorides (Cl total NaCl)	7.32	5.86
Direct alkaline (CO_3NA_2)	1.25	3.26
Ash	8.80	8.574
Na_2O	4.346	3.438
K_2O	0.251	0.317
CaO	0.095	0.162
MgO	0.050	0.073
Fe_2O_3	0.002	?
P_2O_5, total	0.030	0.375
SO_3, total	0.056	0.130
CO_2	0.550	0.90–1.30
Cl	4.448	3.556
$K_2O:Na_2O$	1:17.3	1:10.8

* MESTREZAT, Le Liquide Céphalo-rachidien Normal et Pathologique, 1912, Table 5 p. 170.

Mott (1910) found the CO_2 content of the human cerebrospinal fluid, and also that of the lymph or serum, to be as follows:

	Cerebrospinal fluid, percentage of CO_2	Lymph or serum, percentage of CO_2
By vacuum and heating	10	46
By acid and heating in vacuo	50	50
Difference, representing CO_2 in stable combination	40	4

Zdarek tabulated his analysis of the cerebrospinal fluid withdrawn from a meningocele (370 c.c.) as follows:

	Gms. per 1000 c.c.
Dry substance	10.452
Organic substance	2.096
Ash	8.356
Total albumin	0.768
Ether-soluble substance	0.358
Water-soluble ash	8.220
Anhydrous sulphuric acid	0.048
Chlorine	4.245
Potassium oxide	0.167
Carbon dioxide	0.498
Sodium monoxide	4.294
Oxygen combined with chlorine	0.958
Water-insoluble ash	0.168

Dixon and Cow (1921) injected various organ extracts and drugs into the circulation (testis, epididymis, liver, pancreas, chorioid plexus, histamine, pilocarpine, adrenalin, ovary, intestinal mucosa and posterior lobe pituitary) and tested the action of cerebrospinal fluid subsequently secreted on the isolated uterus and other organs, as well as on the intact animal. They found that the last three had the effect of giving to the cerebrospinal fluid physiological properties of similar character; namely, posterior-lobe pituitary action, the last named being the most rapid in effect. All others had no effect on the pharmacological properties of the cerebrospinal fluid.

Egerer-Seham (1923), using collodion-coated paper and suction, prepared ultra-filtrates of the blood and cerebrospinal fluid. Conclusions were as follows:

"1. The ammonium sulphate test (globulin) is negative in the majority of ultra-filtrates of normal blood serum.

"2. The ultra-filtrates of non-syphilitic blood sera give a reduction of the colloidal gold solution in almost all cases. The same is true of the ultra-filtrates of syphilitic sera.

"3. The ultra-filtrates of normal cerebrospinal fluid give no colloidal gold curve.

"4. The reduction of the colloidal gold solution by ultra-filtrates from syphilitic spinal fluids seems to vary with the quantity of the substance reducing the colloidal gold solution present in the priginal spinal fluid.

"5. The substance giving the Wassermann reaction in syphilitic blood does not seem to be ultra-filterable."

CALCIUM

Halverson and Bergeim (1917) determined that the calcium content of the cerebrospinal fluid is very constant at about 5.0 mgms. per 100 c.c., which is about half the content of the plasma. Repeated drainage does not affect the calcium content.

Kummer and Minkoff (1921) determined that the quantity of calcium in normal cerebrospinal fluid is 0.05 per cent.

Leicher (1922), in 29 cases, found the average calcium content of the cerebrospinal fluid to be about 5.0 mgms. per 100 c.c. and 11.3 mgms. in the serum, regardless of whether there was normal or increased cerebrospinal fluid pressure.

Behrendt (1923) estimated calcium ionization in the cerebrospinal fluid of children, and came to the following conclusions:

"In fluid of average acidity, P_H 7.6 to 7.7, the total amount of calcium is 5.0 mgms. per 100 c.c., of which 20 per cent ionizes; i.e., 1.0 mgm. of calcium ions per 100 c.c. of fluid.

"The calcium content increases with the acidity.

"Diminution in calcium dissociation is caused by bicarbonate and secondary phosphate.

"HPO_4 ions are twice as strong as bicarbonate ions in preventing calcium ionization."

Kasten (1924) found that the addition of calcium to the cerebrospinal fluid in various diseases of the central nervous system and in normal individuals never changed a negative to a positive Wassermann reaction.

CHLORINE

Steiner and Beck (1923) found the chlorine content in normal cerebrospinal fluid (as NaCl) to be 0.68 to 0.72 per cent. They observed that the chlorine content falls during meningitis. The diminution can be demonstrated in most cases in the early stages. A diminution under 0.60 per cent has been found exclusively in the meningitides. Such diminution can, therefore, be valued as a positive differential diagnostic sign. Smaller diminutions (0.60–0.66 per cent) occur occasionally in meningismus. A diminution followed by a rise in chlorine content speaks against tuberculous meningitis.

CHLORIDES

Fontecilla and Sepulveda (1921) found 7.3 gms. per 1000 c.c., the average chloride content in normal cerebrospinal fluid. These authors found chlorides always diminished in meningitis, and

much more so in acute than in subacute and chronic meningitis; the greatest diminution of all was in the tuberculous form.

CHOLESTERIN

Tsuchiya (1914) tested the cerebrospinal fluid in 35 cases for cholesterin. The cases included individuals with general paralysis, dementia praecox, idiocy, epilepsy and manic depressive psychoses as well as normal individuals.

He refers to Pighini (1919) and Mott (1910) finding cholesterin absent in normal persons and present in degenerative diseases of the nervous system.

Chauffard, Saroche and Grigaut (1911) found cholesterin in the cerebrospinal fluid of both well persons and those suffering with central nervous system disease.

Katakura (1914) found cholesterin in the cerebrospinal fluid of cases of brain disease.

Tsuchiya found cholesterin absent in the cerebrospinal fluid in all cases, sick and well. In the blood serum it ranged from 0.010 gm. to 0.023 gm. per 10 c.c.

CHOLESTEROL

Weston (1915) found cholesterol in the cerebrospinal fluid in a series of cases, suffering from various psychosos, in amounts ranging from 0.00305 mgm. to 0.00496 mgm. per c.c. He was unable to discover any constant relation to the type of psychosis, but found it greater in the degenerative types.

CHOLINE

Gumprecht (1900) reported minute quantities of choline in the cerebrospinal fluid and interpreted it as the product of brain metabolism, probably due to lecithin decomposition.

Kopetzky (1912) held the same view of origin, stating further that in meningitis it is increased and is the toxic factor in the disease.

FERMENTS

Cavazzani (1896 and 1900) first showed the presence of glycolytic and oxidizing ferments in the cerebrospinal fluid. He mixed cerebrospinal fluid with starch paste and after twenty-four hours found 0.01 to 0.08 gm. of sugar. This was no proof of fermentation, because Cavazzani found that the cerebrospinal fluid contained normally as much or more sugar.

Kafka (1911) found diastatic ferments in some normal cerebrospinal fluids, but not all, in small quantities, and in larger quantities in cases of paresis, dementia praecox, alcoholism, senility and arteriosclerosis.

He was not able to find amboceptor in the cerebrospinal fluid of pregnant women. He did find in pregnancy amboceptor in transudates and exudates.

Leschke and Pincussohn (1917) made observations on the presence of glycolytic and diastatic ferments in the cerebrospinal fluid. They examined fluid from normal persons and from cases of tabes, paresis, cerebrospinal syphilis, neurasthenia, tuberculosis and arteriosclerosis of the central nervous system, and found small quantities of glycolytic ferment in all conditions. It existed temporarily and was absent on the third day after withdrawal. In 4 cases of diabetes, diastatic ferment was absent. It bore no relation to the cell count. In no case could the passage of the ferment from the blood to the cerebrospinal fluid be demonstrated. The authors believe that this point is important, since it indicates that the cerebrospinal fluid is not a transudation or lymph, but a secretion.

Both in health and in many diseases of the central nervous system, diastatic ferments were demonstrated. The quantity bore no relation to the disease or the cell count.

Immune bodies, such as the agglutinins, according to Sicard and Widal and Lewandowsky, and amboceptors and complements, according to Weil and Kafka, do not pass from the blood through normal meninges into the cerebrospinal fluid.

Concerning the passage of amboceptors from blood to cerebrospinal fluid, the results are contradictory, as found by Abderhalden, Meyer and Kafka.

Amboceptor for placenta was found in the blood of pregnant women but not in the cerebrospinal fluid.

This speaks in favor of the secretory nature of the cerebrospinal fluid and against its being a transudate or lymph.

Lindig (1917) found negative results in 12 or 14 cases in pregnancy as to the passage of amboceptor from the blood into the cerebrospinal fluid. The two positive cases he regarded as due to faulty material and technique.

Mestrezat found no amylolytic power in normal fluid, or only very slight traces. Other authors found this ferment present in hydrocephalic cases. Miller reported proteolytic enzyme absent in

normal fluid. Link and Pollack found a peptolytic enzyme in normal spinal fluids. Galletta found a fat-splitting enzyme in 3 out of 7 cases. Clerc found none. Cavazzani found a glycolytic ferment. Panzar, Lewandowsky and Mott could not corroborate this finding.

No fibrin ferment, alexin or hemolysin is present in normal cerebrospinal fluid (Levinson, 1919).

GLUCOSE (DEXTROSE)

There is in the normal cerebrospinal fluid a sugar, which is dextro-rotary, yields CO_2 by yeast fermentation, reduces copper salts and with phenylhydrazin gives osazone crystals which melt at 205°F. This is dextrose.

The constant proportionate relation of the quantity of this sugar in the cerebrospinal fluid and the blood leaves little doubt as to the source of the sugar in the cerebrospinal fluid. Whether it is directly transferred from the mother liquid to the cerebrospinal fluid as dextrose or passes through a glycogen stage in the cells of the chorioid plexus is not known.

Yoshimura demonstrated glycogen in the vacuoles of the epithelial cells of the chorioid plexus.

Goldmann, by means of intravital staining, discovered in the fetal pig that intracellular glycogen was demonstrable in the chorioid plexus cells and in no other cells of the central nervous system. This substance, unlike the dye, was not held back by the cells but secreted drop by drop and diffused with the cerebrospinal fluid throughout the central nervous system.

The estimation of the sugar in the cerebrospinal fluid in health and disease has been repeatedly done. The following table shows the findings of the indicated workers, in milligrams per 100 c.c. of spinal fluid:

Nawratzki (1902)	55.5	
Mestrezat (1902)	48 to 53	
Kopetzky (1913)	46	
Hopkins (1915)	64 to 90	
Kraus and Corneille (1916)	55 to 110	
Schloss and Schroeder (1916)	54 to 139	
Seham and Nixon	64 to 90	
Von Jaksch	60 to 80	
Levinson (1919)	64 to 90	
Fontecilla and Sepulveda (1921)	50	average
Martin (1922)	44 to 56	average 51.5
Alpers, Campbell and Prentiss (1924)	53 to 84	

From the investigations of these workers it may be stated that the sugar in the cerebrospinal fluid is usually increased in encephalitis and dementia praecox, always in diabetes mellitus. It is usually diminished in acute meningitis, practically always in tuberculous meningitis. Syphilis of the central nervous system in any form has no constant effect on the sugar content of the cerebrospinal fluid.

Hopkins (1915) concluded, in regard to glucose in the cerebrospinal fluid, that "its concentration in health is slightly lower than that of the blood sugar. In meningitis there is the greatest disturbance in the relationship, there being a pronounced hyperglycemia associated with just as pronounced a drop in the sugar content of the fluid, this drop being due evidently to the destructive activity of the invading microorganisms (of 22 cases, 15 were tuberculous). In diabetes the sugar content of the spinal fluid is almost as high as that of the blood. In infections such as pneumonia, there may be a hyperglycemia without apparent change in the spinal fluid."

Weston (1916) estimated the sugar of the cerebrospinal fluid in 20 cases of dementia praecox, 10 of manic depressive insanity, 20 of paresis, 6 of epilepsy and 9 of imbecility. He found individual differences, particularly in the dementia praecox groups, but the averages for the different groups showed no considerable deviation from normal. The average for all cases was 0.0725 per cent. Twenty untreated cases of paresis showed an average of 0.0718 per cent.

Kraus and Corneille (1916) determined the sugar content in 22 cases without organic involvement of the nervous system. They found it to range from 0.055 to 0.110 per cent, the average being 0.0818 per cent. In 21 syphilitic cases the range was identical and the average 0.0915 per cent. There was no correspondence between the amount of globulin, number of cells and the sugar content.

Schloss and Schroeder (1916) estimated the spinal fluid sugar content in 45 normal children, in 23 cases of meningitis, in 10 cases of poliomyelitis and in 8 cases of epidemic meningitis. The normal range was 0.05 to 0.139 per cent. They found the quantity of sugar decreased in meningitis, especially tuberculous meningitis, and not altered in a constant manner in the other two infections.

Coppe (1922) analyzed 95 cerebrospinal fluids and came to the conclusion that the normal sugar content in the cerebrospinal

fluid lies between 60 and 80 mgms. per 100 c.c. He further decided that the tendency to regard a high sugar content as a diagnostic sign of epidemic encephalitis is unwarranted, since just as high a sugar content is found in other nervous diseases. He found that a sugar content below 40 mgms. per 100 c.c. strongly favored infective meningitis, a low estimation being of especial value in tuberculous meningitis.

Kelley (1923) concluded that the average amount of dextrose in the cerebrospinal fluid is 0.055 per cent. He found "that under normal conditions the percentage of sugar in the cerebrospinal fluid is not changed by intravenous injections of dextrose."

Moates and Keegan (1923) made estimations of the sugar content on 203 specimens. They found that the normal range was 0.04 per cent to 0.068 per cent; and that the sugar content was distinctly increased in epidemic encephalitis and diminished by infectious meningitis, and was not co-related to the Wassermann reaction, colloidal gold curve, cell count, globulin or total protein.

Fontanel and Leulier (1924) decided that a sugar index of 0.098 or more in the cerebrospinal fluid signified diabetes mellitus, epidemic encephalitis or hyperalbuminosis.

Alpers, Campbell and Prentiss (1924) estimated 421 spinal fluid sugars. In 13 persons, the sugar content ranged from 50 to 65 mgms. per 100 c.c. In 35 cases of epidemic encephalitis the average was 82 mgms. Sugar was generally increased, and of distinct diagnostic value although not pathognomonic. Twenty-five cases of untreated general paresis averaged 65 mgms. Twenty treated cases of paresis averaged 55.4 mgms. In 21 cases of dementia praecox there was an average of 80.1 mgms., although some cases showed as high a sugar content as epidemic encephalitis. Eleven cases of manic depressive insanity gave an average of 66.9 mgms. Two cases of diabetes mellitus showed 123 and 189 mgms. per 100 c.c.

Kasahara and Uetani (1924), experimenting with normal rabbits, found a decrease in the concentration of the reducing substance in the cerebrospinal fluid after subcutaneous administration of insulin, and a parallelism of the concentration of the reducing substance, both in the fluid and blood, after the administration of insulin. The hypoglycorrhachia attained its maximum between the second and third hour and returned to normal in seven hours.

MAGNESIUM, IRON, ALUMINUM AND CHOLESTERIN

Depisch and Richter-Quittner (1922) found magnesium, iron and aluminum absent in normal cerebrospinal fluid. Cholesterin was also absent.

NON-PROTEIN NITROGEN

UREA. Mollard and Froment reviewed the literature on the urea content in the cerebrospinal fluid, up to 1909. The normal amount of urea in the cerebrospinal fluid, as found by various workers, was as follows:

Widal and Froin (1904)	0.015 per cent to 0.035 per cent
Carriere (1905)	0.001 per cent to 0.015 per cent
Forbes (1908)	0.035 per cent to 0.04 per cent
Castaigne and Weill (1911)	0. to 0.15 per cent
Emery (1912)	0.035 per cent to 0.05 per cent

Mollard and Froment (1909) asserted that normally the quantity of urea in the spinal fluid was negligible, but in nephritis it might increase to a point of diagnostic or prognostic significance. From the study of 23 cases collected at that time they concluded (a) that a notable increase of urea in the spinal fluid could not be considered as pathognomonic of uremia with involvement of the nervous system, since it might be found whenever the kidneys functionated improperly; (b) that a urea content attaining or exceeding 0.4 per cent did not permit of definite conclusions, but should be considered in conjunction with concomitant symptoms.

In 1910 Froment reviewed the literature, included the report of cases in his preceding article with Mollard and collected reports of 34 new cases, making in all 57 reported cases up to 1910.

From the study of these cases, Froment drew the following conclusions:

That all pathological conditions without kidney involvement showed a negligible quantity of urea in the spinal fluid, namely, 0 to 0.015 per cent, and that it never attained 0.1 per cent; while in uremia the content varied between 0.15 and 0.45 per cent; that some cases without a definite picture of uremia showed a definite increase of urea, as, for instance, 0.25 per cent to 0.29 per cent in cases of arteriosclerosis or Bright's disease, in which at necropsy there were found multiple cerebral softenings, cerebral hemorrhages or meningitis; that one could determine the association of retained urea and uremia, even though other pathological

states existed; that with a spinal fluid urea attaining or exceeding 0.4 per cent one could definitely say that a pure or, more rarely, an associated uremia existed, and foretell a nearly fatal outcome. With less than 0.1 per cent of urea the diagnosis of uremia should be rejected. If the urea content of the spinal fluid lay between 0.1 per cent and 0.3 per cent the condition was frequently but not always to be interpreted as a pure uremia, while one could not reject all other diagnoses. Should there be uremia, the prognosis was often favorable.

Javal (1911) established the agreement in urea content in all body fluids. He estimated it in various cases in blood and spinal fluid, blood and pleural fluid, blood and edema fluid, pleural fluid and edema fluid, ascitic fluid and edema fluid, and found it uniformly identical.

Castaigne and Weill (1911) concurred in the identical inferences to be drawn from the urea content of blood and spinal fluid. They decided that urea in the cerebrospinal fluid never reaches 0.1 per cent in normal states.

Widal (1911) confirmed the parallelism of the urea content of blood and spinal fluid. This gives the urea content of the spinal fluid an importance equal to that of the blood.

Nobécourt and Darré (1912) reported 12 spinal fluid urea estimations in children with nephritis.

Nobécourt, Bidot and Maillet (1912) reported 12 more examinations of urea in the spinal fluid of infants. They concluded that a urea content above 0.1 per cent is soon fatal.

Nobécourt, Sevestre and Bidot (1912) reported 14 new examinations of the spinal fluid in infants under one year of age, suffering chiefly from gastrointestinal disorders. They found the urea content in the cerebrospinal fluid of infants under one year with various affections quite variable. It may be normal (0.015 per cent to 0.04 per cent), augmented (0.04 per cent to 0.06 per cent) or greatly increased (0.15 per cent or even nearly 0.4 per cent). They suggest that renal disorder alone is not the sole cause, but that the liver probably plays an important rôle in high urea contents.

Soper and Granat (1914) estimated the urea content of the cerebrospinal fluid in 56 cases in which nephritis was excluded. They found the urea in the majority (48) below 0.06 per cent, although it ran as high as 0.179 per cent. In 21 cases of uremia the urea content was above 0.2 per cent in 13 cases, and between

0.1 per cent and 0.2 per cent in 5 cases, and under 0.1 per cent in 3 cases. They concluded that "a spinal fluid urea content higher than 0.2 per cent indicates a severe uremia and a rapidly fatal termination. A content between 0.1 per cent and 0.2 per cent means a rapidly fatal termination in the majority of cases of nephritis. A content between 0.05 per cent and 0.1 per cent does not permit of any definite conclusions either as regards diagnosis or prognosis. Such a content is, however, suggestive of severe urea retention and must be taken into consideration in the diagnosis of the condition. . . . " They found that the urea content of the blood and cerebrospinal fluid agrees in almost all cases.

Fine and Myers (1914) in 15 cases of chronic nephritis found the concentration of urea in the cerebrospinal fluid to be 88 per cent, creatine 46 per cent, uric acid 5 per cent and sugar 57 per cent of that in the blood.

Woods (1915), in a series of cases of chronic nephritis, was unable to establish any relationship between the retention of any nitrogenous body and the occurrence of albuminuric retinitis. He found the total non-protein nitrogen in the spinal fluid, as a rule, 25 per cent lower than that in the blood. The concentration of urea in the spinal fluid, in relation to the total non-protein nitrogen, was fairly constant throughout, averaging approximately the same percentage at high as at low levels, an average of 78 per cent. He concludes that estimations of total non-protein nitrogen and of urea in the spinal fluid offer no greater diagnostic or prognostic significance than estimations of these substances in the blood.

Mestrezat (1915) offers the following opinion: The normal urea content of the cerebrospinal fluid is 0.06 per cent. Cases of renal impermeability to urea without uremia may show up to 0.1 per cent of urea and occasionally may have a larger quantity without clinical signs. Cases of pure uremia range from 0.098 to 0.634 per cent, and of such cases, those with readings below 0.3 per cent are curable and those above 0.3 per cent are fatal. Cases of clinical uremia in which some other disease is present have been found to show 0.1 per cent to 0.764 per cent of urea. The content of urea present in the cerebrospinal fluid, whether it be normal or raised, is approximately the same as in the blood.

Cullen and Ellis (1915) determined the urea by the Van Slyke and Cullen modification of Marshall's urease method in the spinal fluid and blood in 32 cases of tabes. "In 63 per cent of the deter-

minations the difference between the urea content of the blood and that of the spinal fluid was less than 2 mgms. per 100 c.c. The greatest difference was 11 mgms. per 100 c.c. The urea values varied from 20 to 42 mgms. and from 32 to 46 mgms. of urea per 100 c.c. of serum and spinal fluid respectively. All lie within the possible range of normal variation. The occasional difference between spinal fluid and blood serum may be due to the rapid rise and fall of blood urea in different stages of protein digestion. From the nature of the process of secretion of spinal fluid, one would expect the changes in its urea content to lag somewhat behind those of the blood. The results are in accordance with the already founded view that the animal tissues are, in general, osmotically permeable to urea, which, therefore, tends to reach the same level of concentration in the different body fluids."

Canti (1916) concluded, from the examination of 7 persons in whom there was no evidence of kidney involvement, that the normal urea content of the cerebrospinal fluid is 0.02 per cent to 0.05 per cent. In 20 fatal cases of uremia the urea content ranged from 0.23 per cent to 0.88 per cent.

Leopold and Bernhard (1917) made the following observations on the protein content of the cerebrospinal fluid:

"Chemical examination of the spinal fluid in ten normal cases in children gave the following results: The total non-protein nitrogen varied between 17 and 26 mgms. per 100 c.c. of fluid, the average being 21 mgms.; the urea nitrogen varied between 7 and 13.5 mgms., the average being 9.9 mgms.; the creatinin varied between 0.7 and 1.5 mgms., the average being 0.9 mgm. In no case was there enough uric acid present in the spinal fluid to give a positive quantitative test. The sugar content varied within very narrow limits (0.07 and 0.1 per cent), the average being 0.07 per cent. The figures for the non-protein nitrogenous constituents and the sugar content were lower in the spinal fluid than in the blood, in normal children. The concentration of total non-protein nitrogen in the spinal fluid averaged 75 per cent of that in the blood, the urea 82 per cent of that in the blood and the creatinin 60 per cent of that in the blood.

"1. In chorea the chemical examination of the spinal fluid for its non-protein nitrogenous constituents gave results closely paralleling those obtained in normal children.

"2. Chemical examination in cases of idiocy, syphilis, epilepsy and enuresis gave similar results.

"3. In acute nephritis without uremic symptoms, the total non-protein nitrogen was slightly increased and uric acid was present in small amounts. In acute nephritis with uremic symptoms the total non-protein nitrogen, urea, and creatinin were markedly increased and uric acid was present in slight amounts. The sugar content was also increased. The figures obtained in the analysis of the spinal fluid were lower than those from the blood.

"4. In serous meningitis the non-protein nitrogenous constituents as well as the sugar content were within normal limits. In tuberculous meningitis the total non-protein nitrogen and the urea were normal, but the creatinin was slightly increased. Uric acid was present in every case but the sugar content was normal or slightly reduced. In cerebrospinal meningitis the non-protein nitrogenous constituents were normal, but the sugar content was reduced. In a fatal case of meningitis in which the streptococcus was found, the non-protein nitrogenous constituents were normal and sugar was absent.

"5. In the early stages of infantile paralysis the non-protein nitrogenous constituents as well as the sugar content were within normal limits."

Laurès and Gascard (1920) estimated the urea content in the cerebrospinal fluid in individuals subject to seizures, epileptic and hysterical. During seizures the urea content ranged from 0.15 gm. to 0.70 gm. per 1000 c.c. and, when not having seizures, 0.20 to 0.65 gm. They found urea increased during the seizure in epilepsy and diminished in hysterial seizures in any given individual.

Fontecilla and Sepulveda (1921) decided that the average quantity of urea in normal cerebrospinal fluid was 0.1 gm. per 1000 c.c.

URIC ACID

Cestan, Drouet and Colombiès (1923) estimated the uric acid content in the cerebrospinal fluid of 30 healthy individuals. They found both free and combined uric acid. The quantity of free uric acid was constant, the average being 0.004 gm. per 1000 c.c., the range 0.003 to 0.005 gm. The combined form was variable. The total uric acid content averaged 0.014 gm. per 1000 c.c., but ranged from 0.006 to 0.036 gm.

UROBILIN AND BILIRUBIN

Fontecilla and Sepulveda (1921) found that urobilin and bilirubin were absent in normal cerebrospinal fluid, and that it might remain absent even in severe cases of icterus.

IONS

Pincus and Kramer (1923) determined the average concentration of anions and cations in normal serum and spinal fluid to be as follows (values in mgms. per 100 c.c.):

Material	Ca	P	Cl(NaId)	K	Na	CO_2
Serum	9.6	2.9 (adults) 4.6 (children)	578	20.9	328	55.6
Cerebrospinal fluid	4.6	1.3	712	14.7	351	55.7

CO_2 concentration in c.c. per 100 c.c. at 0°c., 760 mm. Hg pressure.

Concentration expressed in gram molecules per liter:

	Na	P	Ca	Cl	$2(CO_3)$	PO_3
Serum	0.143	0.005	0.0025	0.102	0.032	0.001
Cerebrospinal fluid	0.143	0.004	0.0012	0.124	0.32	0.0006

	Serum	Cerebrospinal fluid
Total concentration of cations	0.150	0.148
Total concentration of anions	0.135	0.157
Product	0.020	0.023

Reaction

Nearly all writers have agreed that the reaction of the cerebrospinal fluid is alkaline. Formerly the methods of testing alkalinity were lacking in standardization. The present-day methods of the determination of the reaction of body fluids may vary but the result is expressed in terms of hydrogen-ion (P_H) concentration, following the work of Sorensen.

Cavazzani (1892) was of the opinion that the alkalinity of the cerebrospinal fluid was one-half that of the blood.

The hydrogen-ion concentration in the blood and the cerebrospinal fluid are very closely related.

To elucidate the significance of hydrogen-ion concentration it may be stated that Levy, Rowntree and Marriott (1915) determined the following values:

$$P_H\ 1 = \frac{N}{10}\ \text{Acid}$$

$$P_H\ 6 = \frac{N}{100{,}000}\ \text{Acid}$$

$$P_H\ 7 = \text{Neutral}$$

$$P_H\ 8 = \frac{N}{100{,}000}\ \text{Alkali}$$

$$P_H\ 14 = \frac{N}{10}\ \text{Alkali}$$

They found the reaction for blood P_H to be 7.6 to 7.8; for blood dialysate, 7.4 to 7.6.

Marriott (1916), working on the alkaline reserve of the blood, reached the following conclusions under these conditions:

Normal	= P_H, 8.4 to 8.55
Moderate Acidosis	= P_H, 8.0 to 8.3
Danger	= P_H, 7.7
Coma	= P_H, 7.3

Bisgaard (1914) concluded that the reaction of spinal fluid is greater than P_H 8.1.

Hurwitz and Tranter (1916) decided that normal cerebrospinal fluid is more alkaline than blood, the difference in the hydrogen concentration of the dialysates of the two fluids being equal to 0.45, the value of P_H for the spinal fluid being 8.11. The value of P_H for blood was 7.66. No change in reaction occurs in syphilis.

Felton, Hussey and Bayne-Jones (1917) stated that the hydrogen-ion concentrations of blood serum and spinal fluid are of approximately the same average, 7.75; range, 7.4 to 7.9.

The inorganic components, chiefly chlorides, phosphates and carbonates, occur in almost identical amounts in both blood serum and spinal fluid, so that there is no reason to suppose they would differ in reaction. While the organic constituents vary, the presence of amphoteric amino-acids and proteins tends to preserve a neutral reaction, as emphasized by Robertson.

McClendon (1918) stated that the alkaline reserve, carbon dioxide tension, and hydrogen-ion concentration of blood plasma and spinal fluid in the same person are practically the same; or more definitely, the alkaline reserve differs by about 10 per cent. The carbon dioxide tension is about the same, since the alkaline reserve is about the same and the total carbon dioxide about the same. The hydrogen-ion concentration in blood and spinal fluid is about the same.

Levinson (1919) investigated the cause of the difference in hydrogen-ion concentration in fresh fluids and those which had stood for a period. He observed the hydrogen-ion concentration in fresh fluids to range from 7.4 to 7.6; whereas after twenty-four hours, fluids which stood uncorked showed P_H 7.8 to 8.6. This difference he established as due to the escape of CO_2 into the air. He stated that the hydrogen-ion concentrations in blood and fresh cerebrospinal fluid are identical.

Guillaumin (1923) determined the alkaline reserve of the cerebrospinal fluid in five young adults at 0°c., 760 mm. Hg pressure, per 100 volumes of liquid, to be from 50.6 to 55.3, average, 53.

Fabre, Ranque and Senez (1920), working on the alkalinity of the cerebrospinal fluid, decided it was due to carbonate and bicarbonate of soda, the latter being largely dependent upon the amount of cellular elements.

Isaacs (1923), working on the alkali reserve of the cerebrospinal fluid, found the average CO_2 combining power, in the absence of nervous symptoms, to be 50.7 volumes per cent:

"The greatest frequency of the normal conditions was between 50 and 58 (52 to 54) and in pathological conditions 40 and 50 (46) for the lowest fraction."

Analysis by Spectrum

Shionoya (1924) studied the absorption spectra of the cerebrospinal fluid and concluded that "a normal absorption curve" can be plotted; that a certain deviation of the curve is proportional to the protein content, and more accurate than tests dependent upon intensity of cloudiness. The curve is apparently not influenced by the Wassermann test.

Cells

Levinson (1921) states that it is agreed that normal cerebrospinal fluid contains only from four to six cells per cubic millimeter, and that all are small lymphocytes. The origin of these cells has not been determined, but he suggests that they are derived from the blood and pass through the walls of the chorioid plexus.

Fontecilla and Sepúlveda (1921) found that normal cerebrospinal fluid contains very few if any cells. When present the relative count is: lymphocytes, 93 per cent; large mononuclears, 2 per cent, and polynuclears, 5 per cent.

Long (1920), Fontecilla and Sepulveda (1921) and Leredde, Rubinstein and Drouet (1922) are convinced that the number of lymphocytes in normal cerebrospinal fluid varies between 0.5 and 1 per cubic millimeter. The latter group consider the presence of 1 cell per cubic millimeter suspicious of an inflammatory state.

The estimations of Petty (1916) and McLean (1922) on the spinal fluid of infants who showed no central nervous disease but had digestive or other mild disorders, indicate that infants may respond to such disorders in a manner not seen in adults. Petty found an average of eleven cells per cubic millimeter in 20 cases, and McLean in 35 cases found 13 showing over twenty cells per cubic millimeter.

Bactericidal Property

The bactericidal power of the cerebrospinal fluid has not been studied to any extent. Cushing and Sladen found the Diplococcus intracellularis in the ventricles and not in the subarachnoid space four months after cerebrospinal meningitis, the patient having hydrocephalus as a sequel of the disease.

Lumbar Pùncture Headache

In view of the apparent continuous secretory activity of the chorioid plexus, the removal of small quantities (5 or 10 c.c.) of cerebrospinal fluid should be an innocuous procedure, in the absence of abnormal mechanical conditions within the cranium, such as tumor.

Such a quantity should be rapidly replenished and doubtless is. Why some individuals develop headache, and others do not, is unknown.

MacRobert (1918) has presented a very plausible explanation; namely, that there is continuous escape of cerebrospinal fluid from the subarachnoid space through the puncture hole into the perithecal space.

Solomon (1924) states that injections of pituitary extract or hypotonic solution will produce an increase of the cerebrospinal fluid pressure and will often give prompt relief to a lumbar puncture headache. In some cases this relief is permanent. In other cases it is temporary, but may be obtained again by a repetition; and in some cases it is without appreciable effect.

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Section II

BIOLOGICAL, CHEMICAL AND PHYSICAL PROPERTIES UNDER NORMAL AND PATHOLOGICAL CONDITIONS

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Chapter IV

THE MECHANISM OF IMMUNOLOGICAL CHANGES IN THE CEREBROSPINAL FLUID

JOHN A. KOLMER, M.D., D.SC.

THE immunology of the cerebrospinal fluid in health and disease has been long a subject of considerable interest and importance, not only from the standpoint of theory and speculation regarding the source and mechanism of immunological changes, but likewise in relation to the natural and acquired resistance of the meninges, brain and cord to infection and examinations of the fluid for diagnostic purposes.

Before undertaking, however, a discussion of the immunological changes in the cerebrospinal fluid in disease and the mechanism of their production, it may first be advisable to make a brief survey of the immunology of the normal spinal fluid and the relation this subject bears to infection of the organs of the central nervous system.

The Immunology of the Normal Cerebrospinal Fluid

It has long been known that antibodies commonly found in the blood are not to be detected in the normal cerebrospinal fluid. For example, that peculiar constituent of the plasma known as complement or alexin, which plays so important a rôle in lytic immunological processes and which is so essential in relation to natural and acquired resistance, is not found in the normal cerebrospinal fluid. The opsonins, which are so vitally concerned in the mechanism of the most important single immunological mechanism of all, namely, phagocytosis, and variable amounts

of which are almost always to be found in the blood for pneumococci, streptococci, staphylococci and many other organisms, are usually absent from the normal spinal fluid. While the majority of adults contain sufficient natural diphtheria antitoxin in their blood to protect them against this disease, none of this antibody is to be found in the spinal fluid. The latter is, of course, of little practical importance because neither the diphtheria bacillus nor its toxin is capable of infecting the meninges, brain or cord, although the latter is believed to affect the cardiac ganglia; but the observation is of interest in connection with tetanus, since the toxin of this disease has a very special and important interest in relation to the spinal cord and the same may be said of the toxins of bacillary dysentery, botulismus and probably some other diseases due principally to exogenous poisons. I have repeatedly found traces of natural antitoxin for tetanus in the blood plasma of human beings whose cerebrospinal fluid even in amounts as high as 5 c.c. showed absolutely no more neutralizing power for tetanus toxin than physiological saline solution, as determined by guinea-pig inoculation tests. Agglutinins and bacteriolysins for typhoid and various other bacilli are likewise usually absent in the normal cerebrospinal fluid; at least, this has been my experience, even in the case of individuals immunized with typhoid vaccine and showing agglutinins in their blood serum in dilutions as high as 1:100.

The Results of the Absence of Immunological Properties from the Normal Cerebrospinal Fluid

It may be stated, therefore, that the normal spinal fluid is usually devoid of those immunological principles known to be present in the blood of all or a large majority of human beings. But of what significance are these observations? Does it mean that the organs of the central nervous system are thereby rendered more vulnerable to parasitic attack or less capable of recovery from infection? Are organisms and their toxins spread broadcast throughout the spinal and cerebral subarachnoid space because the cerebrospinal fluid is lacking in these natural principles of resistance? In the case of those diseases due to direct involvement of the meninges, brain and spinal cord by way of the lymphatics I am inclined to believe that the absence of protective principles in the spinal fluid favors infection. For example, if natural tetanus antitoxin were present

in the fluid, I believe that involvement of the ventral horn cells of the spinal cord would be less likely to occur. In other words, it is a demonstrated fact that free tetanus toxin may be found in the spinal fluid in cases of this disease and apparently may be absorbed into the substance of the spinal cord; at least, it is known that tetanus antitoxin injected subthecally is capable of preventing tetanus or dissociating and neutralizing a portion of the toxin already involving the ventral horn cells and it is reasonable to assume that both toxin and antitoxin in the fluid are capable of penetrating into the substance of the spinal cord. Likewise, if antibodies for meningococci, pneumococci and streptococci were present in the cerebrospinal fluid, I believe that we would more frequently escape the meningitides due to direct extension of these organisms from the mastoid cells, accessory sinuses and lymphatics of the upper respiratory tract. But when organisms are brought to the meninges, brain and spinal cord by the blood one cannot blame this antibody-less state of the cerebrospinal fluid for the resulting infections. For example, the spinal fluid is in no way to blame for infection with the Spirochaeta pallida, nor for tuberculosis of the meninges or for those cases of meningococcus, pneumococcus or influenzal meningitis secondary to bacteriemias. The organism may have a selective affinity for these tissues and effectually overcome what may be a very considerable resistance on the part of the blood and invade and infect the meninges, brain and spinal cord without in any manner involving the question of resistance on the part of the cerebrospinal fluid, even though the principles of resistance were present.

Organisms brought to the meninges by the blood, however, may gradually work their way through the tissues to the free surface of the subarachnoid and pia mater and, finding no resistance to their proliferation in the cerebrospinal fluid may be readily enough distributed through the subarachnoid space of the spinal cord and brain so that the cerebrospinal fluid may become a carrier and distributor of organisms and toxins rather than a fighter of infection by means of natural immunological principles. Strictly speaking, therefore, the lack of natural antibodies in the cerebrospinal fluid is of importance in relation to infection only when organisms or their toxins have actually reached the cerebrospinal fluid and find there no resistance to their presence or proliferative activities. Possibly this state may bear a relation to infection of the meninges by way of the lymphatics; but I cannot understand

how the matter of presence or absence of antibodies in the cerebrospinal fluid bears any relation to resistance to those organisms or toxins brought to the meninges, brain or spinal cord by the arterial blood. This includes the Spirochaeta pallida and most of the other pathogenic agents capable of infecting these tissues, although, as stated, when these incidentally find their way into the spinal fluid, the latter is to be blamed in part for their subsequent distribution throughout the subarachnoid space.

The Absence of Immunological Properties from Other Tissue Fluids

But if the normal cerebrospinal fluid is regarded as a product of secretion by the chorioid plexus and selective filtration by the endothelial cells lining the subarachnoid and the pia mater, we should not expect to find natural antibodies in it any more than we may find them in the normal fluid of the joints, pericardium, peritoneum and other serous cavities, as well as the humors of the eye. I have repeatedly secured sufficient amounts of these fluids during necropsies on human subjects made immediately after death and larger amounts from cattle at abattoirs, for various tests for complement, opsonins, agglutinins and bacteriolysins, with uniformly negative results. In other words, just as the normal epithelium of the kidneys and mammary glands holds back certain constituents of the blood, including the natural antibodies, so likewise the endothelium of the serous cavities, including the subarachnoid space, concerned in the secretion of these normal fluids largely for mechanical functions, fails to pass many of the soluble constituents of the plasma, including the antibodies. Owing to the great physiological importance of the brain and spinal cord, our attention is naturally more frequently and intensely focussed upon the cerebrospinal fluid. I believe, however, that the mechanism of its normal production is quite similar to that concerned in the production of lubricating fluids in other serous cavities, but with this difference: that the chorioid plexus is present as an additional organ for secretion or selective filtration because of the larger amounts of cerebrospinal fluid required for physiological functions. The cells concerned in its production, however, do not normally or naturally permit the passage of antibodies in the plasma; why this is so we do not know and we cannot help but believe that Nature is defective in this particular instance.

Immunological Conditions in the Cerebrospinal Fluid in Disease

Are antibodies to be found in the cerebrospinal fluid in disease, and if so, by what mechanism are they produced? With the exception of syphilis our information on these subjects is rather meager because we do not usually secure cerebrospinal fluid for purposes of study and investigation unless there is an indication or possibility of an involvement of the central nervous system. According to the results of examinations of cerebrospinal fluid from cases of diphtheria, scarlet fever, pneumonia, typhoid fever, etc., which I have been able to make for complement, natural diphtheria antitoxin and various opsonins, bacteriolysins and complement fixing antibodies, the general statement may be made that acquired antibodies are not to be found in the spinal fluid regardless of their concentration in the blood unless there is some involvement of the meninges. My associates and I have also attempted passively to transfer antibodies from the blood to the spinal fluid in dogs without success, unless the normal inhibitive secretory mechanism of the cerebrospinal fluid was disturbed by intraspinal injections of serum, broth or some such irritant. In other words, the mechanism holding back normal or natural antibodies is likewise capable of doing so when these antibodies are greatly re-enforced by the immunizing processes of disease or vaccination. I believe the same is true of the renal epithelium, the endothelium of the large serous cavities and to some extent of the glandular epithelium of the mammary glands. In other words, these excretory or secretory cells do not normally allow the antibodies of the blood to pass on, regardless of their concentration in the plasma, providing the cells are in a normal condition and there is no active or passive hyperemia.

In the presence of vascular changes, however, this selective inhibitory mechanism is disturbed. Thus in the ascitic fluid of cardio-renal-hepatic disease, traces of various blood antibodies are occasionally found and especially the reagin of the Wassermann reaction; likewise, in the pleural and pericardial fluids of cardiac decompensation, as well as in the milk, traces of antibodies are to be found during the first few days or weeks of lactation when the glands are especially hyperemic. In other words, transudates in the large serous cavities may contain small amounts of various antibodies, probably due primarily to some physical

mechanism or transudation of plasma constituents as a result of excessive hyperemia and to a lesser extent of excessive secretion or excretion sufficient to break down selective inhibition. In the sterile cerebrospinal fluid of human beings with acute meningeal congestion, erroneously designated as "serous meningitis" or "meningismus" and developing during alcoholism, pneumonia, measles and whooping-cough, I have occasionally found natural anti-sheep hemolysin and traces of complement doubtless carried over into the cerebrospinal fluid from the blood as a result of the acute vascular disturbances.

In acute and chronic meningitis one may find in the cerebrospinal fluid traces of complement, anti-sheep hemolysin and opsonins, but usually in surprisingly small amounts considering the degree of disturbance. In a study of cerebrospinal fluid from cases of meningococcus and pneumococcus meningitis, I was so impressed with the frequency with which no complement at all was to be found in the fluid that I advise and frequently practise the addition of sterile guinea-pig serum to the immune serum prior to subthecal injection for the purpose of activating the bacteriolysins and re-enforcing the bacteriotropins of the immune serum and thereby enhancing curative activity.

Immunological Properties of the Cerebrospinal Fluid in Syphilis

Probably the most marked alteration in the antibody content of the spinal fluid occurs in syphilis. Whence are derived the reagins or antibody-like substances responsible for the Wassermann reaction, the precipitation of colloidal lipoids, gold, mastic, benzoin, etc.? Why is it that the blood of a syphilitic may yield a negative blood Wassermann reaction when the spinal fluid may react positively? It is my opinion that the antibody-like substance responsible for complement fixation in the Wassermann test is identical with that causing the precipitation of lipoids in colloidal suspension in the Sachs-Georgi, Vernes, Kahn and a host of similar tests and reactions described from time to time during the past eighteen years. I also surmise that the same antibody-like substance is responsible for the precipitation of colloidal gold, colloidal mastic, etc., and that it is a reactionary product of the lymphocytes and fixed tissue cells in direct contact with the antigenic substances elaborated by the Spirochaeta pallida; if this is true, Neisser's term "reagin" would appear to be a particularly appropriate

name for this substance because it does not seem to be a true antibody in the sense of being destructive for the Spirochaeta pallida. At least, my colleagues and I have demonstrated the Wassermann reaction in chancre fluids many days before it was found in the blood and it is my opinion that the antibody-like substance responsible for all of these reactions is a product of the admiring circle of cells surrounding depôts of spirochetes and that it is possible for its being produced wherever the parasites are located, including the meninges, brain and spinal cord. If such is true, one may expect to find in the cerebrospinal fluid a large production of the reagin in cases of syphilis of the central nervous system, the amount varying with the degree of infection, being largest in paresis because of the numerically heavy infection and smallest in tabes dorsalis because of the sparsity of spirochetes and more limited involvement of meninges and spinal cord. As would be expected, the blood serum of a majority of the cases of neurosyphilis also yields a positive Wassermann reaction because it is known that the majority of cases also have a syphilitic infection of the cardiovascular or other systems; but it sometimes happens that the blood Wassermann is negative while the cerebrospinal fluid reaction is positive. Whenever this happens, I have surmised that the visceral involvement, as of the myocardium, aorta or other tissues, is so light and latent that detectable amounts of reagin are not being thrown into the blood, while the heavier infection of the meninges, brain or spinal cord produces more reagin in the cerebrospinal fluid. Too much emphasis, however, must not be placed upon propositions of this kind, for many such instances can be explained on purely technical grounds since we may use five to ten times more spinal fluid than serum for conducting the Wassermann test. This increases the sensitiveness of the test with the cerebrospinal fluid because its content of protein and inorganic salts is so much lower than that of serum that the degree of precipitation of colloidal lipoids, with consequent absorption or fixation of complement, is not reduced.

Contrary to the usual impression and expectation, there is a limit to the amount of serum that one may employ in the complement fixation test for securing reactions of the maximum degree of specificity and sensitiveness. Offhand, one may surmise that 0.4 c.c. of serum will give a stronger reaction and detect traces of syphilitic reagin when 0.1 or 0.05 c.c. fail to do so; but, curiously enough, the inorganic salts or proteins of the serum tend to inter-

fere or reduce the degree of complement fixation in syphilis so that a large amount of serum may give a weaker reaction than a smaller amount and, indeed, may even yield a falsely negative reaction. I know this is the case with my new syphilis complement fixation test, and it constitutes the most important single reason for testing all sera in graded and varying amounts instead of in a single amount; at least two different doses should be employed in order to reduce this biological error to a minimum. With cerebrospinal fluid, however, the necessity for using varying amounts in the Wassermann test is not present, and in general terms the larger amounts always yield stronger reactions than smaller amounts. It is a safe general rule that in any method at least five to ten times more fluid may be used than serum, with a consequent increase of sensitiveness. Furthermore, cerebrospinal fluid may be used without preliminary heating at 55°C., since complement requiring inactivation is not present; this adds to the sensitiveness of the reactions since some syphilis reagin is always lost by the process of heating, and for this reason I have reduced the period for heating sera from thirty to fifteen minutes at 55°C. in our new test. Finally, the cerebrospinal fluid is less likely to contain natural anti-sheep hemolysin which may contribute in a small way to an increase of sensitiveness of the Wassermann reaction, although in paresis considerable amounts of this hemolysin and traces of complement may be present in the fluid as detected by the Weil-Kafka reaction.

Conclusions

In conclusion, this brief and incomplete survey of the immunology of the cerebrospinal fluid in health and disease may be summarized somewhat as follows:

1. Normal cerebrospinal fluid does not usually contain the natural or normal antibodies to be found in the blood because of a selective inhibitory mechanism of the cells concerned in the secretion or excretion of the cerebrospinal fluid and in part because this fluid is so frequently renewed.

2. Even when the antibody content of the plasma is greatly increased as a result of immunization by disease or vaccination, antibodies are not usually to be found in the normal spinal fluid.

3. The absence of antibodies in the spinal fluid is of importance in relation to those infections of the meninges by way of the lymphatics and greatly aids the dissemination of infection through-

out the subarachnoid space when the organisms or their toxins have reached the fluid.

4. In acute and passive congestion of the meninges, with serous exudation and transudation, antibodies from the plasma may be passed into the spinal fluid, but only in small and irregular amounts.

5. In acute and chronic meningitis traces of antibodies may be found in the cerebrospinal fluid.

6. Under these conditions antibodies reach the spinal fluid probably more as a result of such physical processes as transudation or exudation of plasma from the blood than by any important removal or decrease of the selective inhibitory secretory or excretory mechanism of the chorioid plexus or endothelial cells lining the meningeal spaces.

7. It is highly probable that the Wassermann and other antibody-like substances of syphilis are produced in the meninges, brain and spinal cord as reactionary substances of cells in contact with the Spirochaeta pallida. For this reason the spinal fluid may yield positive Wassermann reactions when the serum reacts negatively; it may also account in part for variations in the serological reactions of the cerebrospinal fluid taken at different times and at different levels; but the cerebrospinal fluid reactions of this kind are more likely to be due to the use of larger amounts, the absence of natural hemolysins and complement and because the fluid is not heated, with consequent reduction in the amount of the complement fixing reagin.

Discussion

The following questions submitted to Dr. Kolmer before the Commission, together with the answers to them, are here reported verbatim.

Dr. Barker: Dr. Kolmer has referred to the local origin of the reagin in connection with the Wassermann test. I should like to ask him if he thinks the increase of the hemolytic amboceptor in general paresis is also due to a local action of the spirochete?

Dr. Kolmer: In reply to Professor Barker's question, I doubt whether we can look upon the presence of natural anti-sheep hemolysin in the spinal fluid as a product of the spirochete of syphilis itself. To the best of my knowledge, no one has demonstrated, on the part of this organism, the production of a hemotoxin. I surmise that the production of hemolysis is due to a disturbance of the chorioid plexus or of a mechanism concerned in the secretion or excretion of the spinal fluid, which permits the passage of the hemolysin from

the blood to the spinal fluid. I have not found the spinal fluid of any individual to contain anti-sheep hemolysin where it was not already present in the blood. If one were to discover the presence of the hemolysin in the spinal fluid, with its coincident absence from the plasma, he would be compelled, I think, to draw the conclusion that it was a product of the syphilitic infection of the brain and spinal cord; but at the present time I believe that we should look upon its presence in the fluid as being a plasma constituent that has gained access to the fluid through the pathological changes due to the disease.

Dr. Barker: I should like to ask Dr. Kolmer this question: In his use of graded quantities of cerebrospinal fluid in syphilitic cases, can he set limits that will distinguish simple cerebrospinal lues from general paresis and tabes?

Dr. Kolmer: In answer to this question I may state, on the basis of our experience, that, as is well known, the strongest complement fixation reactions are observed in paresis. We may obtain, with 0.2 c.c. of fluid in paresis, a strong reaction, whereas in tabes it may be necessary to use five to ten times this amount to elicit this reaction; but to the best of my knowledge, no one has yet been able to base the Wassermann test on what might be called a quantitative diagnostic basis for the different clinical types of syphilis of the central nervous system.

Dr. Jelliffe: There occur in the literature of paresis (and tabes particularly) numbers of statistical statements, along with a few traditionally handed-down beliefs. Thus it is said that only from 2 to 4 per cent of individuals infected by the spirochete subsequently develop paresis. Furthermore, the literature frequently states that, resulting from an infection through one specific puella publica, a high percentage of tabes or paresis has resulted. This raises the question whether specific strains of the spirochete which may be causally related to paresis may be differentiated.

I should like to ask, in view of these conceptions, whether the immunological studies that Dr. Kolmer has made can throw any light upon, first, the causes for the comparatively low incidence of paresis following syphilitic infection, and secondly, do his immunological studies throw any light upon the question of specific reactionability of certain strains of the Treponema pallida?

Dr. Kolmer: This is a very comprehensive question, because, as Dr. Jelliffe has remarked, it solicits an expression of opinion regarding the tissue specificity or affinity of strains of Spirochaeta pallida. Why it is that the brain and spinal cord are involved in some cases of syphilis and not in others, I doubt if we can answer correctly today. In the first place, I believe we must realize that there are in the members of certain families a predisposition to infections of this character. For my own part, as the result of the studies we have made on this subject during the late years at the Research Institute in Philadelphia, I am by no means ready to subscribe to the theory of specificity of strains of the Spirochaeta pallida. I believe that we may explain so-called specificity by other factors.

To me, in syphilis, the question of trauma is always of considerable importance in determining the localization of the Spirochaeta pallida in the tissues, and secondly, the kind of treatment that is given during the early stages.

The work that has been done in Paris has been questioned, as you doubtless know, during the last year or two, through the discovery of a natural spirochetic infection of the genital organs of the rabbit, that might be mistaken for

the lesions produced by Levaditi's so-called neurotropic strain. I really believe that the Spirochaeta pallida locates particularly in those organs that are subjected to trauma, where there are foci of reduced resistance, and that this might be particularly favored during the early stages of the disease when our treatment is defective, either being too deficient to control spirochetic activity or that our treatment—particularly with the arsenicals—may be sufficient more for the stimulation of spirochetic activity than the destruction of the parasites, and that as future experience is gained we may be able to work out more definitely a relation between the kind of treatment given during the early stages of the disease and the incidence of infection of the central nervous system.

I believe that we may better explain the instances of infection of the central nervous system first on the basis of virulence of the strain infecting the individual; secondly, whether or not there are points in the central nervous system of reduced resistance through congenital transmission or by acquired trauma, and thirdly, according to the kind and amount of treatment administered during the early stages of this disease.

We have nothing, however, from the standpoint of immunology to contribute to this subject. I may state, however, that in our laboratory at the present time we are gathering in strains of Spirochaeta pallida; we are immunizing rabbits with them, and we hope shortly to be able to compare the antibody production by different strains of the Spirochaeta pallida to see whether they can be divided serologically, just as the pneumococcus, the meningococcus and the gonococcus have been divided and grouped by serological methods. This work has not yet been completed, but I believe that when it is finished, we shall have far more definite evidence to present than is afforded at the present time by experiments with rabbits.

Dr. Barker: From the standpoint of immunology, has Dr. Kolmer any suggestion to offer as to the mechanism concerned in the improvement of patients suffering from general paresis, when treated by injection with malaria parasites or with the spirochetes of relapsing fever?

Dr. Kolmer: It may be that the remissions that have been ascribed to inoculation with tertian malaria are due to what has been popularly designated during the last few years as the non-specific protein type of reaction. It may be that the protein of the malarial plasmodia or of the spirochete of relapsing fever, furnishing a foreign protein responsible for the temperature and the leucocytic changes, may be the medium for repressing spirochetic activity, but there is nothing, so far as I know, in immunology itself to explain the phenomenon.

It may be that the antibody for malaria is destructive for the germ of syphilis, but so far the science of immunology has not furnished any such evidence, and at present I believe we must resort to a search for an explanation of the effects of malaria in some cases of paresis as being due to what we have designated as these non-specific protein reactions, in which the high temperature, possibly the increase of leucocytes and the mobilization of the serum proteases of the plasma are to be looked upon as the curative agents.

Dr. Dana: When one uses a typhoid vaccine there results an intense leucocytosis. Is not this secondary result the process which brings about the change in the disease picture?

Dr. Kolmer: I do not think we are prepared to say that it does all the work, but doubtless the leucocytosis contributes very materially to the end result, because leucocytes contain bacteriolysins, and their consequent destruction in the body releases anti-bacterial substances.

Dr. Strauss: Has Dr. Kolmer any personal experience in the treatment of paresis with malaria, and has he followed the leucocytic reaction in these cases?

Dr. Kolmer: Not in paresis. We have followed out the leucocytic changes in malaria. I, myelf, have had no experience at all with the treatment of paresis by malarial inoculation.

Dr. Strauss: In our experience—and I think others have had the same—there is no leucocytosis following the administration of malaria, nor do we get, as a rule, a leucocytosis when we use other non-specific proteins. Occasionally, yes, but very frequently, no. I thought that the explanation that has been offered for this is that there is no general leucocytosis as the result of this type of treatment, but that there may possibly be a local leucocytosis; in other words, that the leucocytosis which takes place, takes place in the region of the pathological process.

Dr. Kolmer: Is the spinal fluid cell count increased? Could not that be determined by examining the spinal fluid?

Dr. Strauss: I have not done that; I have not examined the spinal fluid, but I know at the hospital where we are treating a great number of cases with injections, for instance, of typhoid bacilli intravenously, I have had the cases watched rather carefully for leucocytosis, the blood being examined anywhere from one to eight hours following the injection and the chill, and we do not find any leucocytosis. I did in one case, but in the majority, no. In the malarial cases, we do not find that it occurs. I believe that it is possible for the leucocytosis which occurs to take place where a perivascular infiltration in the brain is existent.

Dr. Aycock: What structure or structures does Dr. Kolmer consider to be the barrière hémato-encéphalique? And at what point is this barrier disturbed by the intraspinal injection of serum, for example?

Dr. Kolmer: I would like to reply that the intraspinal injection of serum or peptone brings about changes in the chorioid plexus, but I can only state that, as the result of our experiments with rabbits and dogs, we have not been able to elicit morphological changes in the chorioid plexus other than a slight degree of hyperemia. Though I have no conclusive evidence to support my belief, I am of the opinion that the injection of these substances into the lumbar sac produces a sufficient degree of congestion of the meninges to account for the occurrence of the spinal fluid changes by an increased exudation or transudation from the plasma of the blood.

Dr. Fremont-Smith: At what point do spirochetes or other organisms brought by the blood, enter the cerebrospinal spaces? Should spinal fluids contaminated with small amounts of blood be inactivated for the Wassermann test? Should fluids from acute meningitis be inactivated?

Dr. Kolmer: I believe we must answer the first question, "according to the organism." The spirochete of syphilis, for example, as is well known, invades the perivascular spaces, and I believe from these locations, particularly when they are quite superficially located, they may readily enough find their way into the cerebrospinal fluid, being aided by the transudation or exudation

of plasma from the vessels, particularly. I believe for this reason we may expect, as has been demonstrated frequently, to find spirochetes in the spinal fluid in the early stages of syphilis, even before there are sufficient tissue changes to produce symptoms.

Regarding the second and third question about the inactivation of spinal fluid, I do not regard this as necessary, even in the case of purulent fluids-because the amount of complement present in the fluid is apt to be so small as to be negligible from the standpoint of the complement fixation test.

Chapter V

EXAMINATION OF THE CEREBROSPINAL FLUID FROM DIFFERENT LOCI

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IT is still an exceptional opportunity that makes possible the examination of cerebrospinal fluid obtained elsewhere than from the lumbar sac. While there are still physicians who look upon lumbar puncture as an exceptional procedure, there are very few who will not consider an examination of fluid at some other locus of the cerebrospinal system as extraordinary and unwarranted. Therefore, our knowledge of fluid pathology in different parts of the ventricular-subarachnoid spaces advances slowly and our conceptions of normalcy in these hidden regions becomes in a way a by-product of pathology. And it should be emphasized here that in the case of an ambient fluid, post-mortem study is of limited value and sometimes misleading.

Certain spaces in the ventricular-subarachnoid fluid system have been tapped sufficiently often to warrant an estimate of normal conditions at these loci, and to present in a number of pathological states abnormal findings consistent enough to suggest their diagnostic or therapeutic worth. However, the whole subject of multilocular fluid examination must be considered as in a formative state, and open to constant revision.

The loci, other than the lumbar sac, which are now tapped without too great hesitation, are the lateral ventricles and the cisterna magna, and from examination of the fluid obtained from these three places most of the following conclusions are derived. Other loci, less frequently investigated, are the cerebral subarachnoid spaces, the cisterna chiasmatis (by means of Bériel's[1] orbital puncture) and the cervical and thoracic spinal subarachnoid spaces. Information of value may be obtained by a single puncture at any of these loci, but synchronous punctures at two or more loci are usually found to be much more valuable. Particularly are

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combined ventricular-lumbar, cisternal-lumbar and double lumbar punctures carried out without difficulty.

Normal Fluid in Ventricle, Cisterna Magna and Lumbar Sac

From our research we believe that the following represents normal relations in these three loci: The pressure is similar in all, i.e., the height of the fluid columns in the manometers is on the same horizontal plane; the fluids are uniformly clear and colorless and do not clot; and cells are absent in the ventricle, although frequently a few are found in cisternal and lumbar fluids under what must be considered normal conditions. The Wassermann and colloidal tests, gold chloride, benzoin and mastic, are uniformly negative.

While globulin (ammonium sulphate ring test) is normally absent in all three loci, slight but constant differences are seen in total protein content, as indicated by trichloracetic acid and sulphosalicylic acid tests, the greatest amount appearing in lumbar, less in cisternal and least in ventricular fluids. While normal figures vary, 30 mgms. per 100 c.c. in lumbar, 25 in cisternal, and 10 in ventricular fluids would be considered as the normal ratio. Comparison is the opposite ratio in regard to sugar content. Sugar is greatest in amount in the ventricular fluid (approximately .08 per cent) and least in the lumbar sac (averaging about .06 per cent), with the cisternal fluid showing a value between these two. Insufficient data are at hand concerning normal values of fluid at other loci.

Fluid from Different Loci in Pathological Conditions

Discussion may most profitably be centered on the examinations in syphilis of the nervous system, brain tumor, cerebral hemorrhage, meningitis, spinal subarachnoid block and tumors of the cauda equina.

1. Syphilis of the Central Nervous System. In general paresis, the fluids from the cisternal and lumbar regions are practically identical; that is, we have never seen a fluid giving pathological reactions from the lumbar sac which did not give similar reactions from the cisterna, with the exception of those cases in which there was a block. Neither have we found a positive cisternal fluid with a negative spinal fluid. It has been noted at times that there is a slight difference in the cell count and in the total protein; however, this difference is relatively slight. There may be a few more cells in the lumbar fluid than in the cisternal

fluid, or the protein content may be a bit higher in the lumbar fluid. Aside from these minor differences, the fluids are the same. On the contrary, there is often a considerable discrepancy between the findings in the ventricular fluid and in the spinal or cisternal fluid, as is shown in the accompanying table (Table 1).

TABLE 1

COMPARATIVE FLUID EXAMINATIONS FROM VENTRICLE AND LUMBAR SAC IN CASES OF GENERAL PARESIS

	Wassermann reaction	Cells	Globulin	Total protein	Gold	Remarks
C. M.						
Lumbar......	Pos. 0.05 c.c.	45	+	++	5555554220	No clinical improvement
Ventricle.....	Neg. 1.0 c.c.	30	0	Normal	5531100000	
Lumbar......	Pos. 0.05 c.c.	14	++	++	3332220000	
Ventricle.....	Neg. 1.0 c.c.	2	+	+	0012200000	
Lumbar......	Pos. 0.05 c.c.	10	+	+	5543332100	
Ventricle.....	Neg. 1.0 c.c.	6	0	Normal	5432100000	
S. G.						
Lumbar......	Pos. 0.8 c.c.*	2	+	+	4443332220	No clinical improvement
Ventricle.....	Neg. 1.0 c.c.	2	0	Normal	1233321000	
R. C.						
Lumbar......	Pos. 0.05 c.c.	......	....	....	5555431000	No clinical or serological improvement
Ventricle.....	Pos. 0.8 c.c.	......	....	....	5431000000	
A. G.						
Lumbar......	Pos. 0.2 c.c.	2	++	+	5555543100	Clinical and serological recovery, four and one-half years' duration
Ventricle.....	Neg. 1.0 c.c.	0	0	Normal	0000000000	
A. F.						
Lumbar......	Pos. 0.3 c.c.	0	++	+	4444221000	Clinical and serological recovery. Clinical recovery lasted over seven years
Ventricle.....	Pos. 0.3 c.c.	1	+	+	4443221000	
Lumbar......	Pos. 0.1 c.c.	5	+++	++	5555553300	
Ventricle.....	Pos. 0.1 c.c.	3	+	+	5555533000	
Lumbar......	Pos. 0.3 c.c.	6	++	++	5555321000	
Ventricle.....	Pos. 0.3 c.c.	0	+	+	5532210000	
H. P.						
Lumbar......	Pos. 0.6 c.c.	18	++	+++	5555544330	A good clinical remission was obtained and the spinal fluid made nearly negative. Treatment stopped, clinical and serological relapse and death
Ventricle.....	Neg. 1.0 c.c.	2	+	+	5543200000	
Lumbar......	Pos. 0.2 c.c.	27	++	++	5555555542	
Ventricle.....	Neg. 1.0 c.c.	7	+	Normal	5555542000	
Lumbar......	Pos. 0.2 c.c.	39	+++	+++	5555532100	
Ventricle.....	Neg. 1.0 c.c.	0	±	+	5555321000	
Lumbar......	Pos. 0.2 c.c.	32	++++	+++	5555555210	
Ventricle.....	Neg. 1.0 c.c.	2	0	Normal	5552100000	
Lumbar......	Positive	13	++	+++	5554430000	
Cistern......	Positive	18	++	+++	5554433200	

* Considerable treatment preceded these tests which were taken at time of first ventricular injection.

In cases of general paresis in which the spinal and cisternal fluids give a typical paretic reaction, the ventricular fluid may be quite normal, or one or several pathological reactions may be found, varying, however, in intensity from the reactions obtained in the spinal fluid. This may be true when a number of examinations are made at intervals. Thus, in the case of a typical paretic, we find on four separate ventricular fluid examinations, made during a period of two and a half months, that the Wassermann reaction was always negative with 1 c.c. of fluid. There was just a trace of globulin and possibly the slightest increase in total protein. The cells varied from 0 to 7. The gold reaction in all four tests gave a paretic curve. In the spinal fluid examination the Wassermann was always strongly positive. Globulin and albumin were markedly increased, and the cell counts varied as follows: 18, 27, 39, 32. The gold always gave a strong paretic curve, much stronger than in the ventricular fluid. Subsequent comparison of the cisternal and lumbar fluid from this case showed always practically identical reactions.

In another case the ventricular fluid gave a positive Wassermann reaction, as did the spinal fluid. There were nine cells in the ventricular fluid, eight in the spinal fluid, but no globulin, only normal albumin, and a negative gold in the ventricular fluid, contrasted with increased globulin and albumin and a strong paretic gold curve (5555530000) in the lumbar fluid.

Similarly, with patients undergoing treatment, the changes in fluid content, apparently dependent upon therapy, do not run parallel in the ventricular and spinal fluids. In our experience, whenever there is a difference between the ventricular and spinal fluids, the spinal fluid is always stronger than the ventricular fluid. In cases undergoing treatment, we find changes occurring in the ventricular fluid from one time to another, similar to what one finds to be true of the spinal fluid, the ventricular fluid being weak on one examination and on the next one strong and again weaker. However, there need be no correspondence between the changes occurring in the ventricular and spinal fluids. We have not been able to draw any clinical conclusions as to the course or prognosis of the case from the characteristics of the ventricular fluid. That is, the cases with a strongly positive ventricular fluid do not seem to have a different course than do the cases with a negative ventricular fluid.

In this connection it is interesting to note that Weigeldt[2] finds no such abnormalities in the ventricular fluids of five paretics, but does occasionally find a positive Wassermann.

Acute syphilitic meningitis is not a very common type of syphilitic affection. However, in 3 such cases we have adequate examinations to show that, as in the chronic form of neurosyphilis, general paresis, so in acute syphilitic meningitis, involvement of the ventricle is not uncommon, although the evidence of pathology is less striking than in the cisterna or lumbar sac (Table 11).

Table 11

Syphilitic Meningitis

	Point of puncture	Color, etc.	Cells	Protein, mgms. per 100 c.c.	Sugar, mgms. per 100 c.c.	Wassermann	Gold sol
Mr. P., 21 yrs. Before treatment..	Lumbar	Opalescent, slightly yellow	1500	236	34	Pos.	
Next day, 21 c.c. Swift-Ellis serum by lumbar puncture 18 hrs. previously.	Right lateral ventricles	Slightly turbid, slightly yellow, fine clot	1246	81	54	Pos.	4433554311
Next day, 21 c.c. Swift-Ellis serum by lumbar puncture 18 hrs. previously.	Lumbar	Turbid, slightly yellow, large clot	1460	400	30	Pos.	3444445532
Mr. R., 23 yrs. Meningeal symptoms, 3 wks. Primary, 8 mos. (?) ago.	Right ventricle	Cloudy, small clot	750	285	...	Neg.	5555554322
	Lumbar	Cloudy, fine clot	....	857	...	Pos.	5555555321
Mr. H. Recent meningeal symptoms with choked disks.	Ventricle	Cloudy	50	154	..	Pos.	2222111000
	Lumbar	Cloudy	174	237	..	Pos.	5555555321

It appears from the above tables that these two types of neurosyphilis, primarily cerebral affections, frequently show abnormal findings in all three loci, differing only in intensity, but that the pathology is uniformly more marked in the subarachnoid space than in the ventricles.

Meningovascular Syphilis, Spinal Type. A number of interesting points are brought out by study of this group. All were submitted to combined puncture because the possibility of spinal subarachnoid block was suggested by the clinical findings. Block was demonstrated in four cases and laminectomy was performed in three. Two of these showed syphilitic lesions as the cause of the block. In Case 4 the block disappeared following antiluetic treatment (Table III).

Table III

Cases of Late Syphilis of the Nervous System in Which Spinal Subarachnoid Block Was Demonstrated by Manometric Studies

CISTERNA MAGNA

Case No.	Color	Cells	Protein, mgms. per 100 c.c.	Wassermann	Gold sol
1. Cervical hypertrophic meningitis*	Colorless	0	68	Neg.	
2. Latent lues, arachnoid fibroma*	Colorless	..	35	+	0455555555
3. Gumma of spinal cord*	Colorless	28	68	Neg.	0014211000
4. Syphilitic meningitis	Colorless	6	42	+	0000000000

LUMBAR SAC

Case No.	Color	Cells	Protein, mgms. per 100 c.c.	Wassermann	Gold sol
1. Cervical hypertrophic meningitis*	Clear yellow	6	800	Neg.†	001221000
2. Latent lues, arachnoid fibroma.*	Clear yellow	14	760	Anti-Comp.	0004555555
3. Gumma of spinal cord*	Colorless	8	178	Neg.†	0002341000
4. Syphilitic meningitis	Clear lemon	24	90	+	0000112100

* Diagnosis is confirmed by operation.
† Previously positive.

Case 2 is of special interest because the cause of the block was found and removed and proved to be an arachnoid fibroma. Subsequently, the block having been removed, the fluid findings were still found to be characteristic of syphilis, strong evidence that we are here dealing with two entirely different pathological conditions.

Where no block exists, syphilis of this type was found to yield very similar findings in cisterna magna and lumbar fluids (Table IV).

TABLE IV

CASES OF LATE SPINAL SYPHILIS PRESENTING TRANSVERSE MYELITIC SYMPTOMS. SPINAL FLUID PATHWAY PROVED OPEN BY MANOMETRIC STUDIES

CISTERNA MAGNA

Case No.	Color	Cells	Protein, mgms. per 100 c.c.	Wassermann	Sugar	Gold sol
5	Colorless	0	26	+	....	
6	Colorless	44	130	+	....	5555541000
7	Colorless	100	67	+	.054 per cent	0012210000
8	....	23	34	+	....	0000000000

LUMBAR SAC

Case No.	Color	Cells	Protein, mgms. per 100 c.c.	Wassermann	Sugar	Gold sol
5	Colorless	0	44	+	....	
6	Colorless	40	150	+	....	5555554311
7	Colorless	120	138	+	.055	0001333000
8	....	72	43	+	....	0000000000

A third point of interest is the xanthochromia. In only one case of this series does yellow color appear without block. However, we have seen numerous xanthochromic lumbar fluids from undoubted syphilitic cases without evidence of cord compression or compressive myelitis.

It is evident, therefore, that combined punctures are of great help in the proper diagnosis of meningovascular syphilis where there are transverse myelitis symptoms.

2. CEREBRAL HEMORRHAGE. Weigeldt states that in 22 cases in which the subarachnoid spaces of brain or spinal cord showed considerable amounts of blood at necropsy, the ventricles were found to be free from blood coloring matter and even erythrocytes. In only two cases was there slight blood contamination of the ventricle from hemorrhage at the base of the brain. This has been our experience in a limited number of cases. We have seen an equal amount of blood in the cisternamagna and lumbar sac shortly after cerebral hemorrhage, and an equal amount of xanthochromia

in later stages. In determining the significance of the xanthochromia in such cases, we have found that when due to hemorrhage the color is the same, and protein in both of these loci is approximately equal and only moderately increased in amount; whereas, the xanthochromic fluid sometimes found above cord tumors, even as high as the cisterna, is less marked in depth of color and much less in protein content when contrasted with the lumbar fluid.

In hemorrhage into the ventricle there is little difference in the appearance of ventricular, cisternal and lumbar fluids.

3. Brain Tumor. It is said by some authors that there are characteristic findings, particularly the gold sol curve, in brain tumor. We have not been able to demonstrate any abnormality of the lumbar fluid in some cases, or any consistent gold sol curve in others. We have found that the lumbar fluid usually presents increased protein, most frequently about twice the normal amount, but sometimes much more. In this finding we are in agreement with many writers.

In an effort to determine the point at which protein enters the fluid, as a possible aid in localization, a group of cases with brain tumor have been subjected by our colleagues, Doctors Fremont-Smith and Hodgson, to ventricular-lumbar puncture. Their preliminary conclusions are that subtentorial tumors are regularly accompanied by high protein occurring solely in the subarachnoid space, the ventricular fluid remaining normal; that tumors of the cerebral cortex give rise frequently to slight increase in subarachnoid protein, and that tumors in proximity to the ventricles cause an hyperalbuminous condition of the ventricular fluid, which also appears in the fluid from lumbar puncture.

4. Acute Meningitis. Much difference of opinion is to be found in connection with the findings in the acute forms of meningitis, those presumably hematogenous in origin, in which the meningococcus, pneumococcus and streptococcus are chiefly found.

Certain facts appear to be well founded:

A. It seems certain that irrespective of the point of entrance of the organism into the meninges, the subarachnoid fluid, whether taken at the cisterna or lumbar sac, shows early in the disease a similar picture, that is, leucocytes and organisms with only slight increase in protein. The amount of fluid obtainable is increased.

B. Later in the course of infection, perhaps by the seventh day, as the exudate increases in amount, there is a tendency for pus to gather at certain foci in the anterior basal cisterns and in the spinal

meninges. It now becomes more difficult to obtain fluid by lumbar puncture. The examination shows enormous numbers of cells, chiefly polymorphonuclear leucocytes, but organisms are less numerous and cultures may fail of growth. If at this stage the cisterna magna be tapped, a cloudy fluid is obtained showing fewer cells than in the lumbar sac and also less protein but a larger number of living organisms. If the ventricular fluid be examined at this time, it will often show an enormous number of organisms, but few cells.

C. Somewhat later in the infection it becomes frequently impossible to obtain more than a few drops of pus-like fluid from lumbar puncture. The protein and cell count is still higher than before, the sugar has been reduced to zero, but no living organisms appear. A blocking of the meningitic fluid pathways is now apparent. The ventricle is found to contain living bacteria.

The above statements may be said to summarize fairly the impressions conveyed in numerous papers on this subject, and are in agreement with a limited personal knowledge of meningitic fluids. As a corollary to this conception, the introduction of curative sera by the cisternal and ventricular route is now frequently advised and often with therapeutic success. Many points of contention are still open for discussion. By far the most important relates to the source of cerebrospinal infection following or accompanying a septicemia. The older conception held by many was that organisms gained entrance to the subarachnoid space directly from the veins, capillaries or lymphatics. But the argument of Lewkowicz[3] that hematogenous meningitis begins primarily as ventriculitis is worthy of careful study. This worker has boldly tapped the ventricles very early in meningitic infections, instead of postponing this procedure until forced to do so by the development of subarachnoid blocking. With few exceptions he finds the ventricles invaded by organisms early, as well as late, in the disease. From these and many other findings he argues that the bacteria gain entrance to the meninges through the chorioid plexus; and that the meningitis is really only a sequela of ventriculitis. Howell and Cohen[4] both hold the same view and state: "Now we consider it proper to give early intraventricular serum, especially if the fluid withdrawn is turbid, indicating a ventriculitis, which commonly occurs in the first few days of the meningeal stage, if indeed the ventricles may not be the first location attacked." This contention is of such great significance from the standpoint

of serum therapy that it becomes our duty to repeat these observations by careful multilocular examination of the cerebrospinal fluid, especially in the early days of infection.

One thing is forced upon the physician attempting to follow with care the course of a meningitic infection; namely, that no proper conception of the course of the disease is to be had by repeated examinations of the lumbar fluid alone, and that with the further progress of the disease, lumbar fluid analyses become progressively less satisfactory, for the simple reason that the products of inflammation as found in the lumbar sac do not adequately represent the course of the infection throughout the cerebrospinal fluid system.

5. Tuberculous Meningitis. It has been found by a number of observers and by us that the fluid obtained at cisternal puncture may contain more organisms and more cells than that from lumbar puncture.

6. Spinal Subarachnoid Block. Perhaps the most satisfactory use of combined puncture methods is in the detection of spinal subarachnoid block.

The loci to be tapped should depend upon the supposed location of the lesion. If a compression of the spinal cord is suspected, cisternal-lumbar puncture is indicated; if the lesion seems to be distal to the conus, that is, below the first lumbar vertebra, then double lumbar punctures should be performed. In doubtful cases the operator should be prepared to examine the fluid at as many levels of the lumbar sac as are indicated, in conjunction, or not, with cisternal puncture. French writers state that the spinal subarachnoid space may be entered at all levels, and they employ cervical and thoracic punctures apparently with impunity. We have not followed this course, although on a number of occasions we have punctured without hesitation between the twelfth thoracic and first lumbar vertebrae.

Whatever the loci selected for puncture, the object to be attained is to tap the subarachnoid space above and below the lesion. It was shown as early as 1913 by Marie, Foix and Robert[5] that there is marked difference in the spinal fluid above and below a compression of the spinal cord. Further studies have confirmed this fact. It is now apparent that the fluid below a tumor or a level of compression from some other cause presents an increase in protein, at times of extremely high degree; and further, that the amount of protein varies little throughout the cavity below the block.

Above the level of compression the condition is somewhat different. Immediately above the block the protein is found to be abnormal, although much less in amount than that below; this increase in protein lessens progressively, the higher in the spinal canal the fluid is examined; yet even in the cisterna magna an increase in protein may frequently be found (Fig. 1).

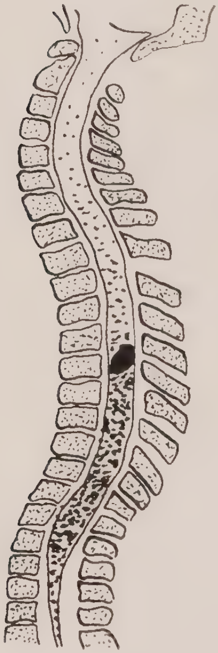

Fig. 1. Diagram to show uniform protein increase below a tumor of the spinal cord. Above the tumor increased protein of less degree is found, which diminishes progressively upwards.

Many of the fluids below a compression of the spinal cord show xanthochromia; a few show the complete Froin syndrome. A great many more are clear and colorless, the only recognizable pathological finding being a hyperalbuminous state. To bring out the significance of increased protein, that is, stasis below a tumor or other compression, a comparison with the fluid above is recommended, together with dynamic studies to demonstrate physiologically a blocking of the spinal fluid pathway. This is readily accomplished by combined cisternal-lumbar puncture, a method that has found advocates not only here but abroad.[6]

7. Tumors of the Cauda Equina. It is not always possible to obtain fluid from below tumors situated low in the lumbosacral canal. In such tumors the fluid directly above has been found to be yellow in color and charged with a large amount of protein. A second puncture above the first will show the protein content less in amount, but even in the cisterna magna an abnormal fluid may be obtained. While such fluids are similar to those found below cord tumors, usually two observations will serve to differentiate them. The amount obtained from above a cauda tumor is large, 10 or 15 c.c., whereas, below a tumor, it is often impossible to get as much as 5 c.c.; and, most important, there is no evidence of block of the spinal fluid pathways as demonstrated by the manometers, both being above the tumor.[7]

That increased protein, even when accompanied by xanthochromia, with absence of signs of block, is not a reliable guide to

TABLE V

EXAMINATION OF CEREBROSPINAL FLUID IN POSITIVE AND DOUBTFUL TUMOR CASES

XANTHOCHROMIA AND HIGH PROTEIN DIMINISHING THE HIGHER THE FLUID IS EXAMINED SUGGESTS CAUDA TUMOR. THIS FINDING IS NOT, HOWEVER, PATHOGNOMONIC

Tumor found at operation	Point of puncture	Color, etc.	Cells	Protein, mgms. per 100 c.c.	Sugar	Wassermann	Gold sol
J. M. Tumor of cauda equina found at operation	Cisterna	Light yellow, slight clot	0	174	58	Neg.	0223443000
Extended upward to L2 vertebra........................	T 12/L1	Dark yellow, slight clot	2	700	62	Neg.	0122454320
LaR. Tumor, intradural, opposite L2 vertebra							
Sept. 27..	L3/4	Deep yellow, clot	Rare	2187			
Oct. 6, at operation................................	T8 level	Pale yellow, no clot	....	286	..	Neg.	
Oct. 6, at operation................................	T12/L1	Lemon, no clot	....	720	..	Neg.	
No lesions of cauda found at operation							
A. B. Symptoms suggest tumor of cauda equina							
Sept. 4.......	Cisterna	....	4	95	..	....	5554332100
Sept. 18..	T 12/L1	Slightly yellow, clot	11	213	75	Neg. previously	
Sept. 18..	L2/3	Slightly yellow, clot	10	249	70		
J. B. Symptoms suggest tumor of cauda equina.........	Cisterna	Clear fluid, yellow	....	Slightly pos.			
Operation. No pathological lesion of cauda equina...........	Lumbar	Clear fluid, yellow	....	Moderately pos.			
O. L. Symptoms suggest tumor of cauda equina.............	Upper L	Colorless Clot +	3	126	65	Neg.	
No tumor found..	Lower L	Colorless Clot +	..	210	69	Neg.	

the existence of cauda tumor is admitted, but that these findings frequently accompany cauda tumors is equally certain (Table v).

The following summary represents our present use of the spinal fluid abnormalities in the detection and localization of spinal subarachnoid block: (1) In a cord-compression suspect, lumbar puncture is performed and dynamic studies carried out, special emphasis being placed on Ayala's index (ratio of quantity of fluid withdrawn to drop in pressure) and Queckenstedt's sign (compression of the jugular veins). Also a rough protein test is carried out at the bedside. If the fluid is yellow, obtained only in small quantity, shows no pressure-rise on jugular compression and contains an enormous amount of protein, then we feel safe in considering it a "compression fluid." (2) If the fluid be clear and colorless, normal in amount, shows a pressure rise, although perhaps delayed, on jugular compression, and contains only a moderate excess of protein, then we immediately puncture the cisterna magna, the field of operation having been previously prepared, in order to obtain fluid for comparison and in order to carry out more accurately our dynamic studies. (3) If we find a block, partial or complete, in a case in which the level is very doubtful, the head is slightly raised and 1 c.c. of lipiodol is injected into the cisterna magna for *x*-ray evidence of the level of block. It has been found that in approximately one-half of the cases cisternal puncture is not necessary, and that in only one-quarter of the cases is lipiodol required.

"Fractional" Examination of the Spinal Fluid

This is the name given by a number of German writers[8,9] to examinations of the fluid when the first and last portions withdrawn are compared. As all who have examined fluids know, there is a slight difference in the first and last portions, even when as little as 10 c.c. are withdrawn. It is found, however, that when the patient is punctured seated and a large amount of fluid is taken, 30 c.c. or more, very striking differences are seen in the first and last tubes. It has been estimated that the spinal canal holds on an average 77 c.c. It is reasonable, then, that, after withdrawal of half of this amount, the findings in the last fluid taken should differ from the first, showing either more pathology if the lesion be mainly cerebral or less pathology if it be chiefly spinal.

In our experience fractional examinations have shown only quantitative differences (indeed, this is all that is claimed for the

method), and the first and last portions are never radically different. We feel, therefore, that the differences shown by combined punctures are much more reliable than fractional examination of the lumbar fluid. However, the fact that fluid pathology changes quantitatively during withdrawal at any locus of the cerebrospinal space is a principle not to be forgotten.

Evidence of Interchange of Fluid at Different Loci

The various experiments of intravital staining by the introduction of dyes into the cerebrospinal fluid spaces, as performed by Weed[10] and others, have shown that substances thus injected are not uniformly distributed throughout the fluid spaces, and tend to gather in one area or another. Experiments by Solomon, Thompson and Pfeiffer[11] showed that if phenolsulphonephthalein was introduced into the lumbar subarachnoid space, with the patient in a horizontal position, it tended to diffuse slowly toward the cisternal region and that very little made its way into the cerebral ventricles. On the contrary, the dye injected into the lateral ventricles tended to make its way into the cisternal and lumbar regions.

Young and Alpers[12] showed by a different method a similar discrepancy between the fluid in the two spaces. They injected Swift-Ellis serum into the lumbar subarachnoid space, the cisternal subarachnoid space and the lateral ventricle. The introduction of this serum leads to the production of an aseptic meningitis. When the fluid was injected into the lumbar subarachnoid space or the cisternal subarachnoid space, it was followed by a rise in protein content and cells in both the lumbar and cisternal regions, but there was little or no evidence that this reaction reached the ventricles. When the serum was injected into the ventricles, it was found that there appeared shortly an increase of these substances in the cisternal and lumbar spaces.

Conclusions

1. The cerebrospinal fluid from various loci may differ in its constituents, even in the absence of evidence of block. This is well shown in cases of general paresis. In cases where interference with movement of the fluid exists, the constituents of the fluid from several loci may be very diverse.

2. Examination of the cerebrospinal fluid from loci other than the lumbar sac is proving of increasing value in our understanding

of a number of pathological states. Particularly do the methods of combined punctures offer diagnostic opportunities impossible from a study of lumbar fluid alone.

3. In the use of therapeutic agents to be introduced into the cerebrospinal fluid, it is often of great importance to take advantage of several possible points of entrance, especially where the possibility of adhesions exists.

Discussion

The following question submitted to Dr. Ayer before the Commission, together with the answer to it, is here reported verbatim.

President Timme: As a point of information in connection with this paper, must one not, in evaluating the presence of certain solids (salt, or protein constituents of the spinal fluid) indicate from what level the fluid was removed, since these solid constituents vary with the level?

Dr. Ayer: My conception of the differences in the fluids at different levels is this: If no block exists, the fluid from the subarachnoid space, cerebral and spinal, is similar, although quantitative differences in the constituents occur. The ventricular fluid is quite different from the subarachnoid fluid. If, on the other hand, there is a block somewhere in the ventriculo-subarachnoid system, then the fluid constituents will vary markedly in different loci, depending upon the location of the block. This is true for all of the substances for which we examine today, whether it be cells or protein, salts, sugar or Wassermann reaction.

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Chapter VI

THE NORMAL AND ABNORMAL QUANTITATIVE PROTEIN CONTENT*

FRANK FREMONT-SMITH, M.D.,† AND JAMES B. AYER, M.D.
WITH THE ASSISTANCE OF MARGARET A. KENNARD, A.B., AND MARY ELIZABETH DAILEY, A.B.

DENIS and Ayer (*Arch. Int. Med.*, 1920, xxvi, 436) described a method for the quantitative determination of protein in the cerebrospinal fluid. This method, essentially unchanged, has now been in use routinely for more than six years at the Massachusetts General Hospital. Ayer and Foster (*J.A.M.A.*, 1921, lxxvii, 365) reported a series of 429 quantitative protein determinations based on the examination of more than 2000 fluids. This paper deals with 622 fluids from 411 cases (in 35 cases fluid was obtained from two or more loci simultaneously) selected from over 8000 determinations. We have chosen these fluids because in them it has been possible to establish the diagnosis by inoculation, culture, operation or autopsy, and to rule out complicating factors. In other cases the clinical record as well as the spinal fluid findings have been considered, and in every case dynamic studies, and particularly jugular compression, emphasized by Ayer (*Arch. Neurol. and Psychiat.*, 1923, x, 420) have been used to establish patency of the cerebrospinal fluid spaces.

Detailed description of the method will be found in the original paper (*Arch. Int. Med.*, 1920, xxvi, 436). Certain modifications, particularly in the preservation of the protein standard, will be described at the end of Table B, facing page 102. We have found that for fluids with very low protein values, such as normal ventricular fluid, it is preferable to use 1 c.c. of cerebrospinal fluid diluted with 1 c.c. of distilled water rather than 0.6 c.c. of cerebrospinal fluid and 1.4 c.c. of distilled water as originally described. In this way it is possible to use only one standard solution (containing 30 mgms. protein per 100 c.c.) for all fluids. For details and discussion of other protein determination methods, the reader is referred to Greenfield and Carmichael ("The Cerebrospinal Fluid in Clinical Diagnosis," 1925) and Pappenheim ("Lumbar Puncture," 1925).

The method of Denis and Ayer has two important advantages over the other methods in use: namely, the small amount of fluid used, and the short time necessary for the completion of the test. Considering the variety of examinations on a single fluid which may be helpful in reaching a diagnosis, and the small amount of fluid usually available, the quantity of fluid necessary to the performance of a single test becomes an important consideration. The method of Denis and Ayer makes it possible to determine the protein content of a sample of spinal fluid in less than ten minutes, while twenty

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fluids can be examined in less than half an hour. Thus the protein content of the ventricular fluid can be determined while the surgeon is operating, and may be significant in helping to localize a tumor.

Without a series of comparative tests the relative accuracy of our method as compared to others cannot be established. Denis and Ayer state that the method is "accurate to within approximately 5 per cent." The exact magnitude of the error inherent in the method has not been determined, since there is no more accurate method to use as a check. It might seem that the determination of protein nitrogen by the Kjeldahl method would afford such a check. Normal spinal fluid, however, contains much more non-protein nitrogen than protein nitrogen. N. P. N. averages 12 to 18 mgms. per 100 c.c. (*J. Exper. M.*, 1925, xlii, 565), while protein N averages 3 to 6 mgms. per 100 c.c. In a normal fluid, with 25 mgms. of protein per 100 c.c., the total nitrogen might amount to 20 mgms. per 100 c.c., of which 16 mgms. are non-protein nitrogen and only 4 mgms. are protein nitrogen ($4 \times 6.25 = 25$ mgms. protein per 100 c.c.). To obtain this latter figure it is necessary to determine separately the total nitrogen, and the non-protein nitrogen, and then subtract the latter from the former. A combined error of 1 mgm. of nitrogen in the two determinations could introduce an error of 25 per cent into the calculation of the protein.

The possible 5 per cent error mentioned by Denis and Ayer applies to the actual amount of protein present, and not to comparative readings between different fluids. Ten complete determinations, on the same fluid, gave five readings of 34 and five of 35 mgms. protein per 100 c.c.

All methods depending on estimation of the amount of protein precipitated lose accuracy when applied to solutions containing large amounts of protein. When the protein content of spinal fluid exceeds 400 mgms. per 100 c.c., a greater degree of accuracy can be obtained by the more complicated Kjeldahl procedure outlined above (using 4 c.c. of spinal fluid). For all practical purposes, however, a sufficiently accurate figure can be obtained by the method of Denis and Ayer, even when the spinal fluid contains several thousand mgms. per 100 c.c., as in the complete Froin syndrome. Considerable amounts of pigment do not materially affect the results but gross bacterial contamination will give too high protein readings.

The method of Denis and Ayer is as accurate as any that we have seen described, has a wider range, a greater speed of execution and is more economical of fluid. The original difficulty in preserving the standard protein solutions has been eliminated.

The need for quantitative protein estimation is brought out most clearly when lumbar and cisternal or lumbar and ventricular fluids are compared, as in cases of spinal cord or brain tumor. Here significant differences may be so slight that the qualitative tests fail to demonstrate them. In many border-line cases, moreover, the protein may be more than doubled and yet the globulin test (Ross-Jones) be negative. (This indicates the need of a quantitative determination of albumin and globulin, for which we have no adequate method.)

In following the progress of disease, or the effect of treatment, the variations in the protein content of the fluid may be as significant as the cell count; in paresis, for instance, the total protein may remain elevated after all other tests have become normal. Lastly, in most research work involving the chemistry of the cerebrospinal fluid, the quantity of protein present is an important consideration.

A quantitative protein test should be used as a routine method of cerebrospinal fluid examination of equal importance with pressure studies, cell count and the Wassermann reaction.

Until quantitative differential albumin and globulin tests are available, the nature of the protein cannot be exactly determined. Greenfield and Carmichael ("The Cerebrospinal Fluid in Clinical Diagnosis," 1925), with others, state that albumin and pseudo-globulin are present in normal fluids, while in pathological fluids these increase and euglobulin and fibrinogen may also appear, but that the albumin content always exceeds the globulin.

The origin of the protein normally present in the fluid is largely a matter of conjecture. The ventricular fluid contains much less protein than the lumbar fluid—as little as 5 mgms. per 100 c.c. may be found—while the amount in the fluid obtained from the cisterna magna lies between the lumbar and ventricular values. The chlorides and non-protein nitrogen, however, have normally the same values in these three loci, while the content of reducing substances diminishes slightly from ventricular to lumbar fluid. The reason for these variations has not been determined, but it is probable that they are dependent, in part at least, upon the fact that the ventricular fluid is derived almost wholly from the chorioid plexus, only a minimal portion coming from the perivascular spaces, while by the time the fluid reaches the lumbar region an appreciable portion of perivascular fluid from brain and cord may have been added. It is possible that the protein present in normal ventricular fluid comes through the chorioid plexus from the plasma, or that it is a product of the ependymal cells. It probably represents the minimal portion of perivascular fluid which enters the ventricles. In any case the total amount is so slight that the ventricular fluid may be considered practically protein-free and the chorioid plexus as normally impermeable to protein.

According to the above suggestion, the increasing protein found as one approaches the lumbar region may be due to the increased number of perivascular spaces emptying into the subarachnoid space. It is possible, however, that arachnoid cells, lymph spaces within the nerve roots and the central canal of the cord may be sources of protein.

In view of this uncertainty as to the origin of the protein normally found in the cerebrospinal fluid, it is impossible to come to definite conclusions in regard to the source of the increased protein found in pathological states. All the possible sources mentioned for normal protein and, in addition, transudation through dilated meningeal vessels may be responsible (Cushing and Ayer, *Arch. Neurol, and Psychiat.*, 1923, x, 167).

The amount of protein normally present in the lumbar fluid varies between 15 and 45 mgms. per 100 c.c. (method of Denis and Ayer). Mestrezat (*Ann. de l'Inst. Pasteur*, 1924, xxxviii, 719) considers 15 to 30 mgms. as normal, while values over 35 mgms. are high. Eskuchen ("Die Lumbalpunktion," 1919) gives 20 to 30 mgms. as normal.

The determination of the upper limits of normal is fraught with many difficulties. Levinson ("Cerebrospinal Fluid in Health and Disease," 1923) uses "normal" to mean fluids which are neither luetic nor meningitic. Since the highest protein values are found in just such cases, i.e., below cord tumors, such use of the term "normal" is unjustified. There is great need for the establishment of true normal values; i.e., fluid obtained from healthy individuals at different age epochs, free from disease of the

central nervous system, and also from any other pathological process which can affect the physicochemical equilibrium between plasma and tissue fluids. Unfortunately, no such series of normal fluids is available. Probably Mestrezat's ("Le Liquid Céphalo-Rachidien," 1912) forty-six fasting patients who were about to undergo operation for hernia, etc., under spinal anesthesia are the nearest approach to such a group. In them the protein content varied from 6 to 32 mgms. per 100 c.c., with an average of 19 mgms. Only three were outside the limits of 13 to 30 mgms. So small a series, however, cannot establish the limits of normal. We have fluids from 13 patients, eighteen to sixty-six years of age, who presented no evidence of organic somatic or central nervous system disorder and in whom dynamics, cell count, globulin, gold sol and Wassermann tests were normal.

The group is made up largely of functional nervous patients who, because of vague symptoms, had lumbar puncture performed in order to exclude neurosyphilis. We cannot state with assurance that any of these cases was strictly normal, since pathological lesions of the central nervous system may not be recognizable clinically.

A much larger group of cases present apparently normal protein values, but to them we have not been able to apply even the criteria used in these 13 cases. From such data we have come to feel that the normal range does not differ greatly from our "normal" series. There is no evidence, in adults, of an age variation in protein content.

We have encountered an occasional case with a protein content of 60 or even 80 mgms. without any apparent cause, and we cannot, therefore, exclude the possibility that occasionally a normal fluid will contain this amount of protein. Any fluid with a protein content of 60 mgms. per 100 c.c., or more, is probably abnormal, and values between 45 and 60 mgms. in the large majority of cases accompany central nervous system pathology.

Our data on "normal" values in cisterna magna fluid and ventricular fluid have been obtained almost wholly from cases with tumor of the cord or brain respectively, and cannot be taken as establishing normal values in these loci. Our impression is that the normal range in the ventricles is from 5 mgms. or less to 15 mgms., while in the cisterna magna it is from 10 to 25 mgms. per 100 c.c.

The amount of fluid withdrawn may modify the protein content, since when large quantities are removed the last few cubic centimeters will represent fluid which has come from the base of the brain, or even from the ventricles, and hence give lower values than the first fluid removed. In our cases the protein was determined on the first 10 c.c. of fluid. In pathological cases repeated punctures at frequent intervals will often, for the same reason, give progressively lower values.

We have tabulated our cases (Table A) and publish for comparison with them the 429 fluids (Table B) taken from the paper of Ayer and Foster *J.A.M.A.*, 1921, lxxvii, 365). These data are presented as an effort towards establishing limiting values for various diseases. It will be seen that great variations exist, which may depend in part upon the stage and severity of the process.

Since the protein content of the fluid taken alone has relatively little clinical significance, we shall not discuss these groups in detail. Small groups presenting correlated clinical data and relatively complete cerebrospinal fluid examination will subsequently be published.

Chapter VII

THE NORMAL AND ABNORMAL QUANTITATIVE SUGAR CONTENT*

FRANK FREMONT-SMITH, M.D.† AND MARY ELIZABETH DAILEY, A.B.

THIS preliminary report on the cerebrospinal fluid sugar content is based upon the study of 425 spinal fluid and 150 whole blood or plasma sugar determinations made at the Massachusetts General Hospital during the past year. Folin and Wu's latest modification for blood sugar[1] was the method used, the spinal fluid, protein-free filtrate being prepared as recommended for blood plasma. The final dilutions were made in the modified sugar tubes recommended by Rothberg and Evans.[2]

In 1852 Deschamps and Bussy[3] found a reducing substance in the cerebrospinal fluid escaping from the ear of a patient with a fractured skull. In 1897 Nawratski[4] proved that the cerebrospinal fluid contained glucose.

I. Relation of the Spinal Fluid Sugar to Blood Sugar

The relation of the spinal fluid sugar to blood sugar has been a disputed subject. That the spinal fluid sugar is high and sometimes equals the blood sugar in diabetes mellitus is well known. Several Japanese investigators[5,6,7] during the past five years have shown that in dogs and rabbits the spinal fluid sugar follows the blood sugar changes after a latent period.

On the nature of the relation of the cerebrospinal fluid sugar to the blood sugar in man there is little agreement. For example, Wittgenstein in 1923[8] concluded that the spinal fluid sugar level is independent of the normal fluctuations of the blood sugar, the spinal fluid sugar representing 50 to 80 per cent of blood sugar, while Polonovski and Duhot[9] found blood and spinal fluid sugar values parallel and sometimes identical, both during fasting and following hyperglycemic and hypoglycemic reactions. The blood

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† Aided by grants from the Ella Sachs Plotz Foundation and the John White Brown Scholarship.

sugar was usually higher than the spinal fluid sugar. A special method of protein precipitation was used, hoping thus to get rid of possible non-dialyzable portions of the blood sugar, which they suggested might account for the higher blood sugar figures.

Reducing Substances in Blood and Cerebrospinal Sugar

The idea that the reducing substances in the blood may not be all glucose is not new. In 1922 Folin and Berglund,[10] from the results of hydrolysis on the sugar content of whole blood and plasma filtrates, concluded that there are present in the blood, more especially in the plasma, reducing substances which disappear after hydrolysis, and therefore cannot be glucose. This non-glucose fraction at times amounted to over 10 per cent of the so-called blood sugar.

That an appreciable fraction of the total reducing substance which we measure as blood sugar is not glucose complicates the study of the relation of blood sugar to spinal fluid sugar and at once raises the question whether all the spinal fluid reducing substance is glucose.

In twenty-five instances we have hydrolyzed spinal fluid filtrates, using Folin and Berglund's technique. In the majority of the cases the spinal fluid sugar values have decreased after hydrolysis, this non-glucose fraction varying from 1 per cent to 15 per cent of the total. In a few instances the sugar content increased. In the tests with blood our results were similar to those of Folin and Berglund, the change in sugar content of blood and spinal fluid usually being parallel. Further studies are in progress.

This indicates that in the spinal fluid as well as in the blood plasma there are usually present reducing substances other than glucose which may disappear on hydrolysis and may amount to over 10 per cent of the total measured spinal fluid sugar.

Comparison of the Sugar Content in the Spinal Fluid and the Blood

In a small series we have found the sugar in the ventricular fluid somewhat higher than in the lumbar fluid. This agrees with the observations of Cestan, Riser and Laborde.[11] The cause of this difference has not been established.

The sugar in the ventricular fluid, although somewhat higher than that in the lumbar fluid, is not so high as the blood sugar. That the blood sugar is nearly always higher than the spinal fluid

sugar is the one point on which most observers agree. The non-glucose fraction of the plasma sugar does not account for the difference, since that fraction may be present in the spinal fluid in about the same percentage as in the blood plasma. The explanation for the higher blood sugar is not forthcoming at present. It is possible that the cells of the chorioid plexus utilize a portion of the sugar transmitted through them.

The weight of evidence, then, indicates that the spinal fluid sugar is derived from the blood sugar and is in some way dependent on it. This may be accepted in the absence of evidence to the contrary.

Rise in the Cerebrospinal Fluid Sugar Following an Increase in the Blood Sugar

It will be seen that if the spinal fluid with its sugar content is formed in the ventricles, the speed with which the ventricular fluid will reflect blood sugar changes will depend in part on the rate of formation of the fluid. On this point no reliable data are at hand, but it is probable that the hourly production in man is somewhere between 5 and 30 c.c. A transient high blood sugar can directly affect only that portion of the cerebrospinal fluid which is newly formed during the hyperglycemic period. The ventricular fluid formed during such a period, with its higher sugar content, must then be mixed with fluid previously and subsequently formed and, after an unknown period, depending on the fluid circulation and diffusion rate, reach the lumbar sac. It will not be surprising, then, to find little immediate change in the sugar content of the lumbar fluid following rather definite blood sugar increases. The Japanese workers already referred to[5,6,7] observed a latent period in dogs and rabbits, even though the fluid was removed from the cisterna magna.

We have obtained simultaneous spinal fluid and blood samples during sugar tolerance tests on four patients, three epileptics and one case of degenerative disease of the cord. The glucose was given once intravenously and three times by mouth. In these latter cases the spinal fluid sugar rose only 3, 4 and 6 mgms. per 100 c.c. respectively during a period of fifty minutes, while the plasma sugars rose from just above 90 to 144, 160 and 162 mgms. per 100 c.c. When glucose was given intravenously, the plasma rose from 111 mgms. fasting to 290 mgms. at the end of ten minutes and then gradually fell. The spinal fluid collected at intervals of ten minutes showed no appreciable change for seventy minutes, at which time

the blood sugar had fallen to 140 mgms. Twenty minutes later, or one and one-half hours after the intravenous injection of glucose, the spinal fluid sugar had increased a total of 9 mgms., while the falling plasma sugar had reached 99 mgms., which was 10 per cent lower than at the beginning of the test. It should be remembered that such slight rises in spinal fluid sugar are no greater than normal differences between lumbar and ventricular sugar, and as there is a considerable quantity of fluid removed during such a test, the last sample may represent fluid which was in the ventricular system at or near the beginning of the test.

This indicates that for an hour or more after the administration of glucose, hyperglycemia is not accompanied by any significant rise in the lumbar spinal fluid sugar. That the lumbar fluid sugar does, however, respond to blood sugar changes in man after a latent period is indicated by the results of sugar tolerance tests continued over a period of several hours. The following case is an example of such a delayed response to blood sugar changes:

A seven year old boy with acute nephritis had a series of convulsions beginning at 7 A.M. Blood was taken at 9 A.M. during the seizure, at which time the sugar content was 312 mgms. per 100 c.c. A little later the convulsion ceased. At 1 P.M. the blood sugar was 200 mgms., while at 4:30 P.M. the plasma sugar was 122 mgms. Spinal fluid withdrawn at this time had a sugar content of 136 mgms., appreciably higher than the plasma. Without the knowledge of the earlier marked hyperglycemia we should have been at a loss to understand a spinal fluid sugar 10 per cent higher than the coincident blood sugar.

A few days later the patient had more convulsions. Blood taken at the onset showed a sugar of 174 mgms. Two hours later, during the convulsion, the plasma sugar was 319 mgms. Lumbar fluid taken at this time showed a sugar of 107 mgms. Here we have in the same patient on one occasion a spinal fluid sugar of 136 mgms. with a coincident plasma of 122 mgms., a few days later a spinal fluid sugar of 107 mgms., while the plasma sugar is 319 mgms. per 100 c.c. In the first instance we had a rapidly falling blood sugar which had been very high; in the second, the blood sugar had climbed to 319 mgms. within two hours and the spinal fluid sugar had had but little time to respond. Fasting blood sugars on this patient on other days were normal.*

Before we can reach conclusions in regard to the normal relationship between blood and spinal fluid sugar, it becomes necessary, then, to know the blood sugar content, and preferably the plasma sugar value, also, since it is from the plasma that the interchange takes place, not only at the time of the lumbar puncture but also for an as yet unknown period preceding the withdrawal of fluid.

*This case has been reported in detail by Metcalf, K. M., and Moriarty, M., *Am. J. Dis. Child.*, Chicago, 1926, xxxi, 65.

The lack of consideration of these various factors and our present imperfect knowledge of the relationship of the cerebrospinal fluid sugar to the blood sugar whence it is derived, explains the disagreement in the literature as to the normal spinal fluid sugar values, which range from 50 to 134 mgms., as given by Schloss and Schroeder in 1916,[12] to much narrower limits, 55 to 65 mgms., set by Mestrezat[13] in a paper published a few months ago.

Cases Illustrating Relation of Cerebrospinal Sugar to Blood Sugar

In considering the sugar content of 318 spinal fluids wherein the clinical diagnosis was established, 57 had values between 80 and 160 mgms. With 21 of these, simultaneous blood sugars were taken and 20 were found to be high. This indicates that hyperglycemia rather than central nervous system changes was responsible for the high spinal fluid sugar. The diagnoses in this group included such varying conditions as brain tumor, brain abscess, uremia, carbon monoxide poisoning, epidemic encephalitis, meningism, cerebral vascular accidents, central nervous system syphilis, fluid removed under ether and fluid obtained after intravenous glucose. Sixty-four fluids had sugar below 50 mgms., and of these, 59 were cases of acute meningitis, including tuberculous and acute purulent syphilitic meningitis. In the 5 remaining fluids with low sugar content, there were marked cellular reactions. In 7 of this group of sugar contents below 50 mgms., coincident blood sugar estimations ranged from 99 to 155 mgms. per 100 c.c., indicating that these low spinal fluid sugar values were independent of the blood sugar level. This is in accordance with the findings of Kelley[14] who showed that inoculation of spinal fluid with bacteria and subsequent incubation caused the sugar to diminish.

The remaining 197 fluids with sugar values varying from 50 to 80 mgms. were obtained from patients presenting a variety of conditions, such as central nervous system syphilis, brain tumor and abscess, early tuberculous and early acute purulent meningitis, poliomyelitis, epidemic encephalitis, and cases where there was no evidence of central nervous system disease. In these cases simultaneous blood sugars were obtained in 49 cases, only 7 being above 125 mgms. We are unable to say that any of these cases are normal, although we feel that normal fasting values will fall within this group.

Conclusions

Our conclusions to this preliminary report are as follows:

1. Spinal fluid as well as blood plasma contains reducing substances other than glucose, which disappear on hydrolysis and which may amount to more than 10 per cent of the total measured "sugar" content.

2. The hyperglycemia produced by sugar tolerance tests is reflected in the lumbar spinal fluid only after a latent period following the administration of glucose, by which time the blood sugar may have fallen to below the spinal fluid sugar level.

3. Because of these facts no statement can be made at present as to the normal ratio of spinal fluid sugar to blood sugar, nor can the normal limits of spinal fluid sugar be given.

4. Spinal fluid sugars above 80 mgms. occur in a great variety of conditions as well as in epidemic encephalitis. Such sugars are usually associated with hyperglycemia, which is not uncommon in cerebral conditions.

5. In the absence of hypoglycemia spinal fluid sugars below 50 mgms. nearly always indicate an acute infection of the meninges.

6. Sugar values in the cerebrospinal fluid between 50 and 80 mgms. occur where no pathology of the central nervous system exists, but may also be found in such differing conditions as early acute meningeal infections, epidemic encephalitis or brain tumor.

7. Spinal fluid sugar should be determined on patients fasting, preferably over night, and then compared with coincident blood sugar determinations.

Discussion

The following questions submitted to Dr. Fremont-Smith before the Commission, together with the answers to them, are here reported verbatim.

Dr. Patterson: Has Dr. Fremont-Smith made any observations on the spinal fluid sugar in epilepsy?

Dr. Fremont-Smith: We have made very few observations of the sugar content in the spinal fluid in epilepsy. Three of the cases on which we did some sugar tolerance tests were epileptics. The sugar contents in those cases varied from between 55 and 82 mgms.

Dr. Ordway: Has any work been done on the spinal fluid sugar or chloride content in chorea?

Dr. Fremont-Smith: We have had no such cases, and I have not seen any references in the literature.

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Note. Since this went to press, two important articles have appeared, bearing on the relation of spinal fluid sugar to blood sugar:

Goodwin, G. M., and Shelley, H. J. *Arch. Int. Med.*, Chicago, 1925, xxxv, 242.

Kubie, L. S., and Schults, G. M. *J. Exper. M.*, N. Y., 1925, xlii, 565.

Chapter VIII

THE NORMAL AND ABNORMAL QUANTITATIVE CHLORIDE CONTENT*

FRANK FREMONT-SMITH, M.D.† AND MARY ELIZABETH DAILEY, A.B.

IN view of the importance, both diagnostic and theoretical, attached to the chloride content of the cerebrospinal fluid we present this preliminary report.

In our experience the normal chloride content of the human cerebrospinal fluid varies between 720 and 750 mgms. per 100 c.c. (expressed as NaCl), as determined by the method of Van Slyke.[17] Mestrezat[1,2] gives 725–740 mgms. per 100 c.c. as the normal limits and considers quantities below 720 or above 750 mgms. per 100 c.c. as pathological. Eskuchen[3] finds that the normal variation lies between 725–750 mgms. per 100 c.c. In this series it was found that an individual, fasting and at rest, will have normally the same chloride content in lumbar, cisternal and ventricular fluid, which is in agreement with the results of Cestan, Riser and Laborde.[4] Normal blood plasma values range between 570 and 620 mgms. per 100 c.c.[5]

Comparison of Cerebrospinal Fluid Chlorides and Blood Plasma Chlorides

The much higher chloride content of the spinal fluid as compared with that of the blood plasma has been associated with the almost complete absence of colloids in the spinal fluid, both by Mestrezat[1,6] and by Depisch and Richter-Quittner,[7] the high chloride content giving the spinal fluid an osmotic pressure equivalent to that of the plasma.[1]

The low cerebrospinal fluid chloride content in acute infections of the meninges, first recognized by Nobécourt and Voisin,[8] has

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† Aided by grants from the Ella Sachs Plotz Foundation, and the John White Brown Scholarship, Harvard Medical School.

Further publications elsewhere will elaborate the studies already made.

not been satisfactorily explained. Mestrezat,[1] while admitting that the low plasma chloride content is a factor, considers a "local meningeal permeability" more important in allowing equalization between the spinal fluid and plasma chlorides. In this way he interprets the important chemical and pathological studies of Voisin[9] who found the decrease in the spinal fluid chloride value to be proportional to the severity of the meningeal process.

The high chloride content of the cerebrospinal fluid as compared to that of the blood plasma deserves special attention in any consideration of the nature of the cerebrospinal fluid. Our results are in accord with those of Mestrezat whose fundamental studies (see bibliography numbers 1, 2, 6, 10 and 11) have received scant attention by recent writers; and we believe with him that the cerebrospinal fluid can no longer be considered a secretion, but that it is derived from the plasma and dependent upon osmotic and hydrostatic forces for its formation.

Our studies on human cerebrospinal fluid and plasma indicate that variations in the blood plasma chloride value are reflected in the chloride content of the cerebrospinal fluid, a point emphasized by Mestrezat[1] and indicated by the earlier work of Nobécourt and Voisin,[8] but that the quantitative distribution of chlorine ions in the two fluids is dependent, in part at least, upon the difference in their protein content. Thus any increase in protein content of the plasma, such as may occur in dehydration, will increase the difference between the plasma and cerebrospinal fluid chloride (i.e., will increase the quantity of the spinal fluid chloride, the plasma chloride remaining the same), while either a decrease in the amount of plasma protein or an increase in spinal fluid protein will lower the chloride content in the spinal fluid to a level nearer to that of the plasma. Other factors to be considered, but not yet studied in detail are, on the one hand, substances other than protein in the plasma which do not readily pass into the cerebrospinal fluid; and on the other hand, substances pathologically formed in the cerebrospinal fluid, such as lactic acid from the breakdown of glucose, as in meningitis. The former should increase the difference in chloride content between plasma and spinal fluid, while the latter should tend to bring their levels closer together.

In our experience the protein increase in the cerebrospinal fluid in acute infections of the meninges is sufficient to account for only a small part of the marked diminution in the chloride content which so often occurs. In the cases studied to date the amount

of blood plasma chloride was definitely diminished and this, together with the formation of organic acids in the spinal fluid, is the more important element in lowering the quantity of cerebrospinal fluid chloride in acute purulent meningitis and in tuberculous meningitis.

Chloride Content of Cerebrospinal Fluid as a Diagnostic Aid

From a diagnostic point of view the chloride content of the cerebrospinal fluid is valuable, especially when considered in conjunction with the quantity of sugar present.[12] Chloride values below 600 mgms. per 100 c.c. are infrequent in conditions other than tuberculous meningitis, while values between 630 and 680 mgms. per 100 c.c. are commonly found in acute purulent meningitis. Normal or but slightly diminished chlorides would be a strong point against tuberculous or purulent meningitis. Normal quantities are found in epidemic encephalitis and in brain abscess uncomplicated by septicemia or meningitis, while slightly diminished values have been found in a few acute cases of anterior poliomyelitis.

The determination of the sugar and chloride content in the cerebrospinal fluid is of real clinical value. This is in accord with the findings of Mestrezat[1,2] Bickel,[13] Wilcox and Lyttle,[14] Nowicka,[15] Foster and Cockrell[16] and others. Of the two, the sugar seems to be the more important but greater information can be obtained by a combined consideration of both of these constituents.

A low or progessively falling content of spinal fluid sugar (provided the blood sugar is not below normal), together with a very low chloride value (under 620 mgms. per 100 c.c.) and a moderate increase of cells (400–500 per cubic millimeter,) chiefly lymphocytes, is characteristic of tuberculous meningitis. We have not found this combination in any other condition. In acute purulent meningitis the sugar content drops rapidly, usually to under 20 mgms. per 100 c.c. within the first twenty-four to forty-eight hours (in meningitis which is at first localized, i.e., following mastoiditis, the progressive fall in sugar content may be much slower), while in tuberculous meningitis the sugar, which may be normal or even somewhat elevated at the onset, steadily falls, nearly always to below 35 mgms. per 100 c.c. during the first week of the disease, and may drop to 15 mgms. per 100 c.c. or even lower.

A normal or elevated sugar content on two or more occasions at intervals of two or more days, with a normal or but slightly diminished chloride value, would speak most strongly against tuberculous meningitis or acute purulent meningitis.

In epidemic encephalitis, anterior poliomyelitis, brain abscess or tumor, the sugar is always either normal or somewhat elevated; the chloride content is normal except in anterior poliomyelitis, where it may be moderately depressed (670–710 mgms. per 100 c.c.). A mistake should not be made in differentiating these conditions from tuberculous meningitis if the cerebrospinal fluid is examined. Even after several days of observation these conditions may be clinically almost indistinguishable from one another.

Acute purulent syphilitic meningitis is occasionally confusing. The quantity of sugar may fall moderately, thus resembling tuberculous meningitis; but in those cases where the sugar is diminished the cells are much more numerous than is usual in tuberculous meningitis, while the chloride values are but moderately diminished. The Wassermann reaction is necessary to complete the diagnosis. A later publication will present these data on acute infections of the central nervous system in more detail. It should again be emphasized that a combination of pressure and dynamic studies, cell count, color of fluid, presence and character of clot, determinations of the protein, sugar and chloride values, together with a consideration of the stage of the disease, are necessary in order to obtain the most information from a lumbar puncture.

Summary

1. The cerebrospinal fluid chloride content is normally between 720–750 mgms. per 100 c.c. expressed as NaCl.

2. The chloride content of lumbar, cisternal and ventricular fluid is the same.

3. The quantity of cerebrospinal fluid chloride varies directly with the blood plasma chloride content, but the quantitative distribution of the chlorides between the plasma and the cerebrospinal fluid is influenced by the protein concentration of the plasma and of the cerebrospinal fluid; i.e., the greater the difference in the protein between the plasma and the cerebrospinal fluid, in favor of the plasma, the greater will be the difference in the chlorides in favor of the cerebrospinal fluid.

4. Determination of the quantities of chloride and sugar in the cerebrospinal fluid has definite diagnostic importance.

Discussion

The following question submitted to Dr. Fremont-Smith before the Commission, together with the answer to it, is here reported verbatim.

Dr. Maddock: If a low chloride content compensates for a high protein content, do fluids from below spinal cord tumors show a diminished amount of chloride?

Dr. Fremont-Smith: Yes. This diminution in chloride content of the spinal fluid is not appreciable unless the protein content is increased to 300 or 400 mgms. per 100 c.c. In the very high protein fluids below complete subarachnoid block, due to tumor or other cause, the chlorides are markedly diminished.

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Note. Since this went to press, two important papers have appeared concerning the relation of spinal fluid chlorides to plasma chlorides:
Hamilton, B. *J. Biol. Chem.,* Balt., 1925, lxv, 101.
Kubie, L. S., and Schults, G. M., *J. Exper. M.,* N. Y., 1925, xlii, 565.

Chapter IX

A COMPARISON OF THREE COLLOIDAL TESTS, GOLD CHLORIDE, BENZOIN AND MASTIC, UPON THE CEREBROSPINAL FLUID

JESSIE R. COCKRILL*

THE object of this study is to present for comparison the results of 400 reactions of cerebrospinal fluids with the colloidal gold, benzoin and mastic tests.

Lange[1] in 1912 added the colloidal gold test to the diagnostic examination of the cerebrospinal fluid; this test was followed in 1915 by Emanuel's[2] colloidal mastic test which gave further impetus to such colloidal studies. This test was modified in 1917 by Cutting[10] through the addition of potassium carbonate to the saline solution. Results, both favorable and unfavorable, have been contributed by many observers on the value of the colloidal mastic test. In 1920, Guillain and Leçhelle[29] produced the original technique of the colloidal benzoin test, using sixteen test tubes, the dilutions being made with a weak solution of sodium chloride. This technique was repeatedly simplified until a five-tube test was used, the dilutions being made with doubly distilled water. Guillain and Lechelle state: "Cette dernière technique simplifiée nous paraît la plus pratique et la plus recommendable pour le diagnostic rapide de la syphilis du névraxe." They have studied the colloidal gold, the colloidal mastic and the colloidal benzoin test, and observe that the benzoin reaction is simpler and less subject to error than the colloidal gold and more valuable than the mastic test.

In spite of varying observations reported in the literature, the concensus indicates that colloidal tests are an essential part of a complete study of the cerebrospinal fluid.

With this viewpoint the following data, comprising the results of tests made on 400 cerebrospinal fluids from 334 cases, are presented. An effort was made to use the simplest technique with the hope of finding a practical colloidal test for use in the routine

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examination of cerebrospinal fluids. No explanation of the electrochemical, or biochemical, phenomena is attempted. No fluid showing any alteration from its freshly drawn state was used. The fluids studied were those received in the laboratory for routine examination. In these tables only the results of the colloidal tests are recorded, together with the number of cells per cubic millimeter, the quantitative total protein, and the cerebrospinal fluid Wassermann reaction. The clinical diagnosis given in the tables has been recorded after both a laboratory and a clinical study of each case.

The readings of the results of the three colloidal tests are recorded by the usual numerical method used in the interpretation of the colloidal gold reaction. The control tube in the mastic test is represented by the letter x.

Colloidal Tests in Syphilis of the Nervous System. Table vii records 185 tests, showing 3 dissimilar reactions and 182 similar reactions in all three colloidal tests. These fluids were from 139 cases, with an established clinical diagnosis of syphilitic involvement of the central nervous system. There are 11 fluids from cases of general paresis, 41 from cases of tabes dorsalis and taboparesis, 6 from cases of syphilitic meningitis and 127 from cases of "central nervous system syphilis." Seventy-eight of the 139 patients have received antisyphilitic treatment.

Colloidal Tests in Extraneural Syphilis. Table viii gives 44 tests with 5 dissimilar reactions and 39 similar reactions in all three tests. These fluids were from cases of syphilis without central nervous system involvement. The involvement of the central nervous system is excluded in these cases because the clinical signs and symptoms together with the laboratory results were insufficient to establish a final diagnosis of syphilis of the central nervous system. The 44 fluids on the 42 cases show 29 negative reactions in all three colloidal tests; 10 fluids have a positive reaction with the gold, benzoin and mastic tests, all giving reactions of nearly the same intensity.

Colloidal Tests in Miscellaneous Conditions. Table ix shows 20 tests, 2 dissimilar but 18 similar reactions in all three tests. The diagnoses were undetermined after a laboratory and clinical study; the evidence, however, indicated the absence of any syphilitic infection. The Wassermann reaction is negative in all of the fluids. The colloidal gold, benzoin and mastic tests are negative in 16 of the fluids and positive in 2. The benzoin test shows a reaction with 2 fluids in which the colloidal gold and

mastic tests are negative. The colloidal reactions are parallel in 18 of the 20 fluids.

Table X tabulates 151 tests, 6 of which are dissimilar and 145 are similar in all three tests. The diagnoses show a wide variety of conditions. There are 8 cases of meningitis, including 3 meningococcic and 3 tuberculous in character. The colloidal reactions with the three tests are similar but there is no indication of any differential value in the results. The original technique of the benzoin test with sixteen tubes was used in the study of meningitic fluids. The fluids of this table present an interesting variety of colloidal reactions, indicating that such a reaction may occur in any pathological cerebrospinal fluid. This observation coincides with Stanton's[24] statement that "the results of colloidal examinations of the spinal fluid should be considered from a relatively broad aspect and not as a means of pointing conclusively to an anatomic or etiologic diagnosis."

Effect of Time on Colloidal Reactions. In 8 of the fluids (Table XI) the benzoin and mastic tests were repeated after an interval of time ranging from one to six days, inclusive, between the tests, with no appreciable difference in the results. Guillain and Lechelle[29] have repeated the colloidal benzoin test on cerebrospinal fluids kept at laboratory temperature for many days but no appreciable alteration in the results was observed, although Stanton[24] reports that fluids kept at room temperature for forty-eight hours have questionable value. Riddel[37] observed different results in the colloidal gold, benzoin and mastic tests when repeated on the same cerebrospinal fluids. Flesch[49] considered the intensity of the colloidal gold reaction increased when repeated with the same cerebrospinal fluids after an interval of eight days. Kellert[26] found a slightly diminished gold curve with fluids after several weeks at ice-box temperature. Hammes[14] and Oetiker[9] obtained no change in the colloidal curves of fluids kept sterile for eight days, one fluid giving the same curve after one year had elapsed.

Preparation of the Colloidal Solutions. The *colloidal gold solution* was made in the following manner:

A liter of distilled water, containing 10 c.c. of 1 per cent gold chloride and 8 c.c. of a 2 per cent potassium carbonate solution, is brought to the boiling point and 6 c.c. of a 1 per cent formalin solution are added slowly until the appearance of the color. The solution is then removed from the flame and agitated. Every solution used met all of the necessary requirements. Extreme precautions were maintained to have absolutely clean glassware, pure chemicals

and triply distilled water. In making the colloidal gold test one-half of all of the original quantities was used. This has been found satisfactory in 3960 tests.

The technique used for the *colloidal benzoin test* was the simplified one established in 1921 by Guillain and Lechelle.[29] Five test tubes are used: four for the test and one for a control. In the first tube are placed 0.5 c.c. of doubly distilled water which is used instead of saline; 1.5 c.c. in the second, and 1.0 c.c. in the remaining three tubes. Five-tenths cubic centimeters of cerebrospinal fluid are added to the first and second tubes. The 1.5 c.c. of water and 0.5 c.c. of cerebrospinal fluid, in the second tube, are mixed well and 1 c.c. transferred to the third tube, the contents of which are mixed and 1 c.c. transferred to the fourth tube. From this fourth tube 1 c.c. of the mixed fluids is discarded. The following dilutions of the cerebrospinal fluid are thus produced: 1:2, 1:4, 1:8, 1:16. One cubic centimeter of the colloidal benzoin emulsion is then added to each tube and mixed with the contents. One modification was made, it being found unnecessary to heat the emulsion for experimental tests were made using a heated (35°C.) and unheated emulsion, with no alteration in the results. The test is left at room temperature and the readings made after ten or more hours. A stock solution of benzoin was made from which a colloidal emulsion was prepared freshly each time a test was made, the benzoin used being the resin of benzoin and not a commercial powder. Ten cubic centimeters of absolute alcohol were added to each gram of this resin and after forty-eight hours, the clear, supernatant liquid was decanted, the decanted fluid serving as the stock solution. If kept in a tightly stoppered bottle, this remains good indefinitely. Of this, 0.3 c.c. are added slowly to 20 c.c. of doubly distilled water, producing the colloidal emulsion.

One year previous to the observation of the present series of tests, a study was made of the original technique of the colloidal benzoin, as well as its several modifications. At that time it was observed that in cerebrospinal fluids from cases of clinically established multiple sclerosis, the reaction was more marked in the dilutions beyond that of 1:16, the final tube of the simplified technique, and was of the so-called "luetic type" of reaction.

The technique used for the *colloidal mastic test* was the original method of Emanuel.[2] Five test tubes are used for each test, the fifth tube being the control. In the first tube are placed 1.5 c.c. of a 1.25 per cent sodium chloride solution, while 1 c.c. is added to each of the remaining four tubes. To the first tube 0.5 c.c. of cerebrospinal fluid are added and mixed well with the salt solution, 1 c.c. of this mixture is then transferred to the second in which the fluids are mixed, and 1 c.c. transferred to the third tube, while from the mixture in the fourth tube 1 c.c. is discarded. The fifth tube receives no cerebrospinal fluid and it should show complete precipitation after the mastic emulsion is added. The dilutions of the cerebrospinal fluid with the saline are 1:4, 1:8, 1:16, 1:32. To each tube is added 1 c.c. of the freshly prepared colloidal mastic emulsion. After mixing the contents of the tubes, the test remains at room temperature for ten or more hours when the readings are made. The stock solution of gum mastic is prepared by dissolving 10 gms. of gum mastic tears in 100 c.c. of absolute alcohol. The solution is then filtered and kept in a dark bottle, away from the light. One cubic centimeter of this stock solution is added to 9 c.c. of absolute alcohol and this solution is then added drop by

drop from a pipette to 40 c.c. of distilled water. It is very important to add the alcoholic solution to the distilled water slowly. This gives an emulsion that is sufficiently stable to give constant results. The 1.25 per cent sodium chloride solution was used without the addition of potassium carbonate. The mastic emulsion used in 68 tests was made with 95 per cent alcohol because absolute alcohol could not be obtained. The results compare with the colloidal gold as favorably as the rest.

Summary and Conclusion

Table XII summarizes the data. *Four hundred colloidal gold, benzoin* and *mastic tests* show 16 *dissimilar reactions* and 384 *similar reactions* in all three tests. Comparing the colloidal benzoin and mastic with the colloidal gold, the results indicate that the benzoin and mastic are reliable tests of approximately equal value. As the technique of the preparation of the benzoin test is simpler, it is the solution of choice in the routine colloidal examination of the cerebrospinal fluid. In special cases such as meningitis and multiple sclerosis, needing the original benzoin test of 16 tubes, the colloidal gold is preferable.

TABLE VI

TABLE SUMMARIZING BIBLIOGRAPHY ON COLLOIDAL REACTION WITH CEREBROSPINAL FLUIDS

	Reactions studied	Notes
1912:		
1. Lange	Gold	A valuable aid in diagnosis of central nervous system syphilis.
1915:		
2. Emanuel	Mastic	11 cases of general paresis, 2 cerebrospinal syphilis, 1 spinal syphilis and 18 non-syphilitic.
3. Miller, Brush, Hammes and Felton	Gold	Technique and discussion.
4. Swalm and Mann	Gold	Questioned specificity of general paresis curve.
5. Solomon, Koefod and Welles	Gold	
1916:		
6. Jacobsthal and Kafka	Mastic	180 fluids. Cases of neurosyphilis, multiple sclerosis and meningitis gave reactions with the mastic.
7. Sachs	Mastic	431 fluids, from cases of general paresis, tabes dorsalis, cerebrospinal syphilis, syphilitic meningitis, syphilis and non-syphilitic patients.
8. Urechia, Jorgulescu	Gold and mastic	54 fluids. Mastic reaction less sensitive than the colloidal gold.
9. Oetiker	Gold	Constant results on repeating test with same fluid.
1917:		
10. Cutting	Mastic	Mastic reaction is simpler to read and compared with colloidal gold is more convincing.
11. Smith, E. R.	Mastic	Information obtained from mastic identical with that from colloidal gold.
12. Immerman	Mastic	Mastic reaction does not determine whether fluid is syphilitic or non-syphilitic.

TABLE VI (*Continued*)

	Reactions studied	Notes
13. Smith, Lowrey	Gold and mastic	268 fluids, from cases of general paresis, tabes dorsalis, neurosyphilis, and meningitis. Mastic has a place in the examination of cerebrospinal fluid.
14. Hammes	Gold	203 fluids, from cases of general paresis, tabes dorsalis and cerebrospinal syphilis. Colloidal gold more delicate than Wassermann. In meningitis the zone affected or the intensity of the reaction was not constant.
1918:		
15. Eskuchen	Gold and mastic	29 general paresis, 52 tabes dorsalis and 30 cerebrospinal syphilis. Gold and mastic of same value in neurosyphilis.
16. Langdon, F.	Gold and mastic	Mastic reaction not as delicate or reliable as colloidal gold; colloidal gold gives differential diagnosis in neurosyphilis.
17. Vogel, Karl	Gold	"Luetic" type of curve in meningitis—no one test alone pathognomonic.
1919:		
18. Rodriguez	Gold and mastic	30 fluids. In majority of cases mastic and gold are of the same value and may be substituted one for the other.
19. Schönfeld, W.	Mastic	Mastic reaction is specific for neurosyphilis.
1920:		
20. Bonsmann, M. R.	Gold and mastic	280 fluids. Mastic reaction in meningitis of "luetic" type.
21. Camp, C.	Mastic	22 general paresis, 49 cerebrospinal syphilis and wide variety of non-syphilitic.
22. Guillain, Laroche and Lechelle.	Gold and mastic	43 fluids. Gold and mastic coincide in 30 tests and differ in 13.
23. Nast	Mastic	Mastic of differential diagnostic value.

TABLE VI (*Continued*)

	Reactions studied	Notes
24. Stanton, J. M.	Mastic	100 fluids. Mastic reaction was never definitely positive when the colloidal gold was negative.
25. Stern	Gold	In neurosyphilis colloidal gold is more valuable than the Wassermann reaction.
26. Kellert, Ellis	Gold	80 per cent of results correct.
27. Moore, J. E.	Gold	In multiple sclerosis 18 of 28 tests gave general paretic curves.
1921:		
28. Keidel, A., and Moore, J. E.	Gold and mastic	Mastic useful when gold test impracticable.
29. Guillain and Lechelle	Gold, benzoin and mastic	The benzoin test is a reaction of syphilis of the central nervous system, and not of a special form of neurosyphilis. Benzoin reaction is simpler and less subject to error than colloidal gold, and more valuable than mastic. Benzoin with tuberculous meningitis gives "une réaction meningitique très speciale."
30. Mazza, Mey, Nino	Benzoin and mastic	110 fluids, from cases of general paresis, tabes dorsalis, cerebrospinal syphilis, syphilis and non-syphilis. Mastic and benzoin do not differentiate neurosyphilis.
31. Benard	Benzoin	In neurosyphilis a negative benzoin reaction with a positive Wassermann occurs, but a positive benzoin with a negative Wassermann occurs very exceptionally.
32. Warwick, M.	Gold	Colloidal gold reaction gave inconstant response to antisyphilitic treatment.
33. Duhot and Crampon	Benzoin	100 fluids. Benzoin reaction agrees in neurosyphilis with Wassermann.
34. Weill, Dufourt, Chahovitch.	Benzoin	Benzoin reaction does not differentiate tuberculous meningitis from any other.

TABLE VI (*Continued*)

	Reactions studied	Notes
35. Sordelli, Rennella.......	Benzoin, gold and mastic	Colloidal gold more sensitive than benzoin and mastic.
36. Thompson, L. J........	Gold	Colloidal gold curve may vary considerably under treatment.
1922:		
37. Riddel, D. O......... 38. Riddel and Stewart...	Gold, benzoin and mastic	130 fluids. The benzoin agreed with the colloidal gold more closely than the mastic. All gave reactions with non-syphilitic fluids.
39. Benedek...............	Mastic	110 fluids, from 19 general paresis, 21 tabes dorsalis, 14 other neurosyphilis, 47 syphilis, 7 meningitis, 2 multiple sclerosis.
1923:		
40. Eicke and Cohn........	Gold and benzoin	Benzoin compared with gold and Wassermann.
41. Mingazzini............	Mastic	100 fluids; central nervous system syphilis; 242 fluids non-syphilitic. Tuberculous meningitis gave inconstant reactions and tumors gave "luetic" type of reaction.
42. Ferraro...............	Benzoin	Colloidal benzoin reaction is not specific for central nervous system syphilis.
43. Werther...............	Mastic	14 general paresis, 32 tabes dorsalis, 23 cerebrospinal syphilis, and 27 syphilis.
1924:		
44. Souques, Blamoutier, DeMassary, Lafourcade and Terris.	Benzoin	Difference between the Wassermann and benzoin a valuable sign in multiple sclerosis.
45. Froment and Sédallian..	Benzoin	Benzoin of diagnostic importance in multiple sclerosis.
46. Dide, Maurice and Fages, G. 47. Dufour..............	Benzoin	Benzoin gave constantly a reaction in the syphilitic zone in multiple sclerosis.
48. Haguenau and Laplane.		Benzoin: "type syphilitique subpositif," in multiple sclerosis.

TABLE VII

NEUROSYPHILIS

General Paresis

Case	Cells per cu. mm.	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions		
				Gold	Benzoin	Mastic
1	17	62	Weak	5553300000	55550	4433x treated
2	8	67	Strong	5555421000	45410	4555x
3	7	80	Strong	5555422100	45550	3444x
4	5	53	Strong	5543210000	45430	4443x treated
5	10	30	Strong	1234200000	13210	1221x treated
6	3	43	Strong	5543100000	54210	5431x
7	13	87	Strong	5555555432	55550	3322x
8	9	89	Strong	5555311100	44540	3343x
9	124	80	Strong	4443210000	22220	1122x
10	7	85	Strong	5554321000	23320	1222x treated
11	9	50	Strong	1222100000	33330	1222x treated
Tabes Dorsalis, Taboparesis						
1	2	45	Strong	1113300000	11220	0121x treated
2	1	27	Strong	0000000000	00000	0000x treated
	2	30	Strong	0000000000	00000	0000x
3	12	62	Strong	4443311000	23210	3443x
	1	61	Strong	4444321000	33310	5555x
4	13	56	Strong	5533330000	55550	5544x treated
	6	57	Strong	0000000000	00000	0000x
	8	57	Strong	0011000000	22110	1111x
5	18	80	Strong	5543331100	55550	5555x treated
	18	87	Strong	0000000000	00000	0000x
	7	52	Negative	0112221000	01110	0111x
	12	36	Strong	0000000000	00000	0000x
	4	64	Strong	0011210000	01210	0121x
	5	60	Strong	0011110000	01110	0111x
6	4	47	Moderate	5554311000	55410	4333x treated
	11	43	Negative	4443210000	44420	5554x
7	33	364	Weak	2444332100	13420	1222x
8	69	50	Strong	0123200000	13100	2322x
	34	32	Strong	5553210000	33110	1111x
	21	51	Strong	1233321000	12100	2221x
	9	39	Moderate	4332100000	34310	1221x
9	23	50	Moderate	2233210000	13110	3321x
10	1	51	Negative	0000000000	00000	0000x treated
11	2	56	Strong	5555521000	25510	4444x

* DENIS, W., and AYER, J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 430.

TABLE VII (TABES DORSALIS, TABOPARESIS—*Continued*)

Case	Cells per cu. mm.	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions		
				Gold	Benzoin	Mastic
	3	80	Strong	5555542100	45310	4322x
12	16	41	Strong	0112320000	01210	1222x
13	13	73	Negative	2431100000	11100	1111x
14	2	35	Weak	1223100000	01110	0110x treated
15	8	59	Weak	0123200000	01210	1221x treated
16	2	63	Negative	4433210000	44310	2221x
17	50	111	Strong	0155444210	45550	4453x
18	13	87	Strong	5555332100	45440	3444x
19	8	114	Strong	1233331100	12330	1222x treated
20	273	87	Strong	0123332100	12330	1222x
21	7	63	Strong	0123432100	12330	1122x
22	40	43	Strong	2222100000	22220	1222x treated
23	118	115	Strong	1234310000	23440	1122x
24	12	182	Strong	5555555321	55550	5555x
25	1	333	Moderate	1232221100	01100	0111x
26	15	45	Strong	4321100000	12310	1111x treated
27	148	154	Strong	4444210000	44420	4444x
Syphilitic Meningitis						
1	11	63	Strong	3333310000	22220	2222x treated
	22	67	Negative	0000000000	00000	0000x
	9	40	Weak	0000000000	00000	0000x
2	8	28	Strong	5333310000	55550	5544x treated
	18	38	Strong	0000000000	11110	1211x
3	224	200	Strong	5555543100	45540	3443x
Central Nervous System Syphilis						
1	3	53	Negative	0000000000	00000	0000x treated
2	8	65	Negative	0000000000	00000	0000x treated
3	11	108	Strong	5555333000	55550	5555x treated
	14	111	Strong	5555221100	55550	5555x
4	2	27	Negative	0000000000	00000	0000x treated
5	32	64	Strong	4222221000	13310	5554x treated
	7	56	Strong	0112100000	22220	2222x
6	20	87	Negative	5553331100	14210	4431x treated
	5	49	Strong	4433210000	34210	3344x
	7	42	Strong	5543321000	45310	4322x
7	7	54	Moderate	0000000000	00000	0000x treated

* DENIS, W., and AYER, J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 430.

TABLE VII (CENTRAL NERVOUS SYSTEM SYPHILIS—*Continued*)

Case	Cells per cu. mm.	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions		
				Gold	Benzoin	Mastic
7	5	133	Strong	1232100000	12210	1122x
8	0	75	Negative	0000000000	00000	0000x treated
9	3	51	Strong	0000000000	00000	0000x treated
10	2	68	Strong	2222100000	55210	4554x treated
11	11	103	Strong	1111100000	12100	1222x treated
	15	89	Strong	1111000000	11100	1210x
	3	85	Strong	2233210000	12110	1122x
	2	108	Strong	1123310000	33330	2222x
12	69	91	Negative	5555555421	24440	5555x
13	45	58	Strong	4433310000	34210	4422x treated
14	38	118	Strong	0000000000	02210	0222x
15	0	40	Weak	2222321000	22220	2221x
	1	47	Negative	0000000000	00000	0000x
16	7	89	Negative	5555531100	35550	5555x
17	3	56	Negative	0000000000	00000	0000x treated
	5	56	Negative	0000000000	00000	0000x
18	12	73	Strong	5554320000	15410	5555x treated
19	4	36	Negative	0000000000	00000	0000x treated
20	4	46	Strong	2111100000	11110	2222x treated
	3	34	Negative	4321100000	12100	1211x
	5	34	Negative	5433210000	44440	4444x
21	6	35	Negative	1111100000	11100	1111x treated
	7	32	Strong	1122100000	23100	1122x
22	2	69	Negative	0000000000	00000	0000x treated
23	26	56	Moderate	5543311000	55210	5533x
24	15	50	Negative	0000000000	00000	0000x treated
25	5	62	Strong	0000000000	00000	0000x treated
	8	89	Strong	0000000000	00000	0000x
	2	54	Strong	5543210000	44310	1232x
26	7	93	Strong	1223310000	23310	1211x
27	1	39	Negative	0000000000	00000	0000x treated
	1	32	Strong	2233210000	33310	2221x
28	11	73	Strong	5555531000	35530	5555x
29	30	71	Strong	0000000000	00000	0000x
30	5	43	Strong	1233210000	22100	1211x
	3	51	Strong	3111000000	43100	2220x
	4	62	Negative	1232100000	01210	0121x
31	3	53	Negative	0000000000	00000	0000x treated
32	3	44	Negative	4332100000	44440	4444x treated
33	43	57	Strong	4443310000	13110	1111x

* DENIS, W., and AYER, J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 430.

Table vii (Central Nervous System Syphilis—*Continued*)

Case	Cells per cu. mm.	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions		
				Gold	Benzoin	Mastic
34	1	40	Negative	0000000000	00000	0000x treated
35	2	57	Strong	1233100000	33330	2221x treated
	12	77	Strong	0112210000	23210	1232x
36	3	65	Strong	0122100000	01110	0110x
	5	49	Negative	0000000000	00000	0000x
37	2	70	Negative	0000000000	00000	0000x treated
38	2	114	Strong	0232100000	01110	0110x treated
	9	85	Strong	1222210000	32100	1222x
	4	148	Negative	1123210000	12210	1211x
39	3	42	Negative	0000000000	00000	0000x treated
40	20	85	Negative	0122100000	12210	1121x treated
41	2	50	Negative	0000000000	00000	0000x treated
42	0	48	Strong	4533210000	55210	2222x treated
43	12	37	Strong	0001110000	01100	0110x
44	33	73	Strong	5555533210	55550	5555x
45	55	44	Strong	0122100000	12310	2332x
46	4	42	Negative	0000000000	00000	0000x
47	11	143	Strong	0112310000	11100	1110x treated
	26	61	Moderate	0012310000	33310	1221x
48	15	64	Strong	0000000000	00000	0000x
49	16	200	Strong	3555544322	45530	2333x
50	4	89	Strong	0000000000	00000	0000x
	9	73	Weak	0122321000	23210	2221x
51	25	56	Moderate	4555310000	44440	4444x
52	16	58	Moderate	2222100000	22210	1221x
53	8	67	Strong	0000000000	00000	00000
54	12	125	Strong	1222210000	12210	1121x
55	...	87	Strong	2544442110	33420	1122x
	7	31	Weak	5533310000	25310	1211x
	10	38	Strong	5544421000	44310	3331x
	12	105	Negative	5555321000	55550	3333x
56	101	62	Weak	4454320000	55530	1211x
57	11	69	Strong	5432100000	23110	1111x
58	9	48	Negative	0000000000	00000	0000x treated
59	2	41	Strong	5554321000	45540	2332x
60	27	45	Negative	0012221000	12220	1122x treated
61	13	50	Negative	0012210000	22220	0122x treated
62	2	40	Weak	0000000000	00000	0000x treated
63	4	33	Negative	0001110000	01110	0012x treated
64	11	60	Negative	0000000000	00000	0000x treated

* Denis, W., and Ayer, J. B., *Arch. Int. Med.*, Chicago, 1920, xxvi, 430.

TABLE VII (CENTRAL NERVOUS SYSTEM SYPHILIS—*Continued*)

Case	Cells per cu. mm.	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions		
				Gold	Benzoin	Mastic
65	11	36	Negative	0000000000	00000	0000x treated
66	8	100	Strong	0000000000	00000	0000x treated
67	3	57	Negative	0000000000	00000	0000x treated
68	8	43	Negative	0000000000	00000	0000x treated
69	2	60	Strong	1123321000	00000	0000x treated
70	8	55	Weak	0000000000	00000	0000x treated
71	25	108	Strong	0123321000	22220	1222x treated
72	1	46	Strong	0000000000	00000	0000x treated
73	28	43	Weak	0000000000	00000	0000x treated
74	1	28	Negative	0122111000	01110	0111x treated
75	3	45	Moderate	0000000000	00000	0000x treated
76	9	27	Negative	0000000000	00000	0000x treated
77	14	75	Moderate	1255210000	12340	0122x treated
78	12	37	Weak	0000000000	00000	0000x treated
79	2	57	Negative	1223210000	12330	0110x treated
80	100	148	Strong	5555543200	55540	2222x
81	1	50	Strong	0000000000	00000	0000x
82	1	77	Strong	0012221000	12220	0111x
83	20	47	Strong	0122210000	01110	0111x
84	3	67	Negative	0122210000	12330	0111x treated
85	60	108	Moderate	4444322000	02330	0022x
86	12	71	Strong	0012210000	22220	1122x
87	76	70	Strong	1233321000	23330	1122x
88	20	100	Strong	1123321100	12230	1122x
89	30	56	Strong	0112211000	12220	0111x
90	2	69	Negative	0000000000	00000	0000x treated
91	5	53	Negative	5543210000	45430	4443x treated
92	0	38	Weak	0000000000	00000	0000x treated
93	0	125	Negative	0000000000	00000	0000x treated
94	13	167	Strong	3333331000	44410	4433x treated
95	7	89	Strong	0121000000	11110	1111x
	13	62	Strong	0012100000	00110	1121x
	4	57	Weak	0011100000	11110	1111x
96	13	108	Strong	3443310000	23530	2342x
97	16	55	Strong	0013210000	01210	0121x treated
98	167	100	Negative	0000000000	00000	0000x

* DENIS, W., and AYER, J. B., *Arch. Int. Med.*, Chicago, 1920, xxvi, 430.

TABLE VIII

SYPHILIS WITHOUT CENTRAL NERVOUS SYSTEM INVOLVEMENT

Case	Cells per cu. mm.	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions		
				Gold	Benzoin	Mastic
1	2	30	Negative	0000000000	11110	1111x
2	2	65	Negative	0000000000	00000	0000x
3	12	49	Negative	1133330000	55550	5555x
4	1	64	Negative	4444210000	55550	5555x
5	0	33	Negative	0000000000	00000	0000x
6	2	53	Negative	0000000000	00000	0000x
7	7	33	Negative	0000000000	00000	0000x
8	66	63	Negative	1124321000	12110	0111x
		60	Negative	1122110000	01110	0121x
9	3	48	Negative	0000000000	00000	0000x
10	1	28	Negative	0000000000	00000	0000x
	1	30	Negative	0000000000	00000	0000x
11	11	49	Negative	0000000000	00000	0000x
12	2	80	Negative	0000000000	00000	0000x
13	2	55	Negative	0000000000	00000	0000x
14	8	26	Negative	0000000000	00000	0000x
15	1	38	Negative	0000000000	00000	0000x
16	3	83	Negative	0000000000	00000	0000x
17	7	26	Negative	0000000000	00000	0000x
18	27	80	Negative	4554320000	55520	3333x
19	2	36	Negative	0000000000	00000	0000x
20	5	26	Negative	3332100000	12220	1221x
21	6	31	Negative	0012210000	12210	1121x
22	11	47	Negative	0000000000	00000	0000x
23	16	34	Negative	0000000000	22110	0000x
24	3	30	Negative	0000000000	00000	0000x
25	1	41	Negative	0000000000	00000	0000x
26	0	27	Negative	0000000000	00000	0000x
27	5	34	Negative	0122200000	01210	0121x
28	1	28	Negative	0000000000	00000	0000x
29	1	18	Negative	0000000000	00000	0000x
30	4	20	Negative	0000000000	00000	0000x
31	2	53	Negative	0000000000	00000	0000x
32	0	40	Negative	0122110000	00000	0000x
33	0	36	Negative	0000000000	00000	0000x
34	3	33	Negative	0012210000	00110	0111x
35	15	74	Negative	0122211100	23330	1222x
36	1	27	Negative	0000000000	00110	0000x
37	3	27	Negative	0000000000	00000	0000x
38	2	45	Negative	0000000000	00000	0000x
39	4	42	Negative	0000000000	00000	0000x
40	2	49	Negative	0000000000	00000	0000x
41	0	95	Negative	0000000000	00000	0000x
42	0	38	Negative	0111110000	00000	0000x

* DENIS, W., and AYER, J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 436.

TABLE IX
NON-SYPHILITIC. NO DIFFERENTIAL DIAGNOSIS

Case	Cells per cu. mm.	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions		
				Gold	Benzoin	Mastic
1	4	47	Negative	0000000000	00000	0000x
2	1	39	Negative	0000000000	00000	0000x
3	6	29	Negative	0000000000	00000	0000x
4	11	26	Negative	0000000000	00000	0000x
5	7	34	Negative	0000000000	00000	0000x
6	2	50	Negative	0000000000	00000	0000x
7	12	53	Negative	0000000000	00000	0000x
8	3	55	Negative	0000000000	00000	0000x
9	1	40	Negative	0000000000	00000	0000x
10	3	45	Negative	0000000000	00000	0000x
11	1	51	Negative	0000000000	00000	0000x
12	1	40	Negative	0000000000	00000	0000x
13	2	50	Negative	0122210000	01220	0110x
14	0	148	Negative	0000000000	00000	0000x
15	1	45	Negative	0000000000	12220	0000x
16	2	20	Negative	0000000000	00000	0000x
17	0	47	Negative	0000000000	01110	0000x
18	0	45	Negative	0111100000	12220	0111x
19	6	33	Negative	0000000000	00000	0000x
20	0	29	Negative	0000000000	00000	0000x

* DENIS, W., and AYER, J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 436.

TABLE X

CONDITIONS OF VARIOUS KINDS

Case	Cells	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions			Conditions
				Gold	Benzoin	Mastic	
				Meningitis			
1	1730	444	Negative	0000113111	34440	4455x	Meningococcus
2	118	24	Negative	0122100000	12220	0111x	Meningococcus: ventricular
	1890	84	Negative	0001322000	01220	1333x	lumbar
3	750	86	Negative	0000000000	00000	0000x	Meningococcus
4	84	125	Negative	1112444210	42110	1222x	Tuberculous
5	....	210	Negative	0012432000	03330	0333x	Tuberculous
6	....	143	Negative	1253210000	35330	3321x	Tuberculous
7	500	140	Negative	0000000000	00000	0000x	No differential diagnosis
8	....	400	Negative	0000123310	00220	0122x	Pneumococcus
				Other Conditions			
1	15	67	Negative	3333330000	12220	3333x	Multiple sclerosis
2	5	44	Negative	0122100000	01220	0011x	Question of multiple sclerosis
3	6	46	Negative	0122000000	12220	0011x	Question of multiple sclerosis
4	1	34	Negative	0000000000	00000	0000x	Paralysis of right internal rectus muscle
5	0	118	Negative	0000000000	00000	0000x	Question of postencephalitic involvement
6	0	40	Negative	0000000000	00000	0000x	Adenocarcinoma of pituitary gland
7	1	71	Negative	0000000000	00000	0000x	Alcoholic gastritis

	0	69	Negative	0000000000	00000	0000x	
8	3	89	Negative	0000000000	00000	0000x	Chronic prostatitis
9	0	34	Negative	0000000000	00000	0000x	Persistent vomiting
10	2	35	Negative	0000000000	00000	0000x	No differential diagnosis
11	0	77	Negative	0000000000	00000	0000x	Temporal lobe cyst
12	2	25	Negative	0000000000	00000	0000x	No differential diagnosis
13	0	89	Negative	1233321000	01210	0111x	No differential diagnosis
14	0	67	Negative	0000000000	00000	0000x	Occupational neurosis
15	1	73	Negative	0000000000	00000	0000x	No differential diagnosis
16	6	46	Negative	0000000000	00000	0000x	Adenomatous hypertrophy of prostate
17	3	35	Negative	0000000000	00000	0000x	Secondary anemia
18	16	56	Negative	0000000000	00000	0000x	Chronic lead poisoning
19	2	36	Negative	0001210000	01210	0121x	Hypertension
20	4	35	Negative	0000000000	00000	0000x	Rhinitis
21	10	91	Negative	0000000000	00000	0000x	Chronic nephritis
22	18	111	Negative	0000000000	00000	0000x	Peripheral paralysis of seventh cranial nerve
23	8	77	Negative	0000000000	00000	0000x	Epileptiform attacks
24	1	42	Negative	0000000000	00000	0000x	Question of lead poisoning
25	3	121	Negative	0000000000	00000	0000x	Complete left hemiplegia
	2	118	Negative	0000000000	00000	0000x	
26	1	24	Negative	0000000000	00000	0000x	Parkinsonian syndrome
27	2	56	Negative	5554420000	44440	4444x	Third nerve paralysis on right side
28	1	24	Negative	0000000000	00000	0000x	Ataxia
29	0	57	Negative	0000000000	00000	0000x	Duodenal ulcer
30	6	24	Negative	0000000000	00000	0000x	Pyelitis
	0	40	Negative	0001110000	11110	1221x	
31	3	24	Negative	0000000000	00000	0000x	Indigestion, constipation

* DENIS, W., and AYER, J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 436.

TABLE X (CONDITIONS OF VARIOUS KINDS—*Continued*)

Case	Cells	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions			Conditions
				Gold	Benzoin	Mastic	
32	0	22	Negative	0000000000	00000	0000x	Jacksonian epileptic convulsions
33	3	45	Negative	1232100000	23320	0121x	Deep tumor of brain
	0	58	Negative	5543320000	24550	0122x	
		616	Negative	2455554210	23350	1245x	
34	2	33	Negative	0000000000	00000	0000x	Acute fibrinous pleurisy
35	16	114	Negative	0000000000	00000	0000x	Question of gliomatous cyst
36	13	160	Negative	0000000000	00000	0000x	Pernicious anemia
37	24	114	Negative	1123210000	01110	0110x	Chronic prostatitis
38	0	36	Negative	0000000000	00000	0000x	Hysteria
	0	35	Negative	0000000000	00000	0000x	
39	7	42	Negative	1222211000	01110	0111x	Psychoneurosis
	5	40	Negative	0000000000	00000	0000x	
40	....	...	....	4443210000	44210	3443x	No differential diagnosis
41	0	30	Negative	0000000000	00000	0000x	Optic neuritis
42	1	28	Negative	0000000000	00000	0000x	Psychoneurosis
43	2	51	Negative	0000000000	00000	0000x	Bulbar palsy
44	0	41	Negative	0000000000	00000	0000x	Hydrocephalus
45	27	800	Negative	1123322000	01110	1111x	Arteriosclerosis; hypertension
46	2	55	Negative	0122100000	12210	1221x	Trigeminal neuralgia
47	12	30	Negative	0000000000	00000	0000x	Glioma of brain
48	0	23	Negative	0000000000	00000	0000x	Residual urine, cause unknown
49	3	70	Negative	0000000000	00000	0000x	Psychoneurosis

50	14	47	Negative	0111000000	11000	1100x	Cervical cord tumor
	30	1600	Negative	0000112311	22330	1233x	
51	4	30	Negative	0000000000	00000	0000x	Edema or multiple cortical hemorrhages
52	0	27	Negative	0000000000	00000	0000x	Trigeminal neuralgia
53	1	38	Negative	0000000000	00000	0000x	No differential diagnosis
	0	36	Negative	0000000000	00000	0000x	
54	4	66	Negative	0000000000	00000	0000x	Spastic paraplegia
55	2	45	Negative	0000000000	00000	0000x	Epilepsy
56	1	28	Negative	0000000000	00000	0000x	Question of cerebral arteriosclerosis
57	2	15	Negative	0000000000	00000	0000x	Ophthalmoplegia
58	0	62	Negative	0000000000	00000	0000x	Slight spasticity of legs
59	1	108	Negative	1113210000	11210	1221x	Arteriosclerosis; hypertension
60	0	27	Negative	0000000000	00000	0000x	Idiocy
61	0	28	Negative	1245554221	14440	2444x	Unilateral convulsions
62	6	42	Negative	0000000000	00000	0000x	No differential diagnosis
63	2	33	Negative	1234220000	12100	0111x	Myelitis
64	7	35	Negative	0000000000	00000	0000x	Ptosis of right lid
65	0	33	Negative	0000000000	00000	0000x	Supraorbital neuralgia
66	45	250	Negative	0000130000	00000	0000x	Brain tumor
	9	182	Negative	0000000000	00000	0000x	
	10	180	Negative	0000000000	00000	0000x	
	21	333	Negative	0001133210	32110	1221x	
	15	333	Negative	0001221000	01120	0112x	
67	2	33	Negative	0000000000	00000	0000x	Vertigo
68	8	26	Negative	0000000000	00000	0000x	Question of renal stone
69	0	70	Negative	0000000000	00000	0000x	Paralysis agitans
70	0	50	Negative	0000000000	00000	0000x	Combined sclerosis
71	3	91	Negative	0000000000	00000	0000x	Arteriosclerosis; right facial palsy

* Denis, W., and Ayer, J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 436.

Table x (Conditions of Various Kinds—*Continued*)

Case	Cells	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions			Conditions
				Gold	Benzoin	Mastic	
72	4	200	Negative	1122331000	23210	2221x	Sensory aphasia
73	1	67	Negative	0000000000	00000	0000x	General arteriosclerosis
74	4	51	Negative	0000000000	00000	0000x	Vertigo
75	2	47	Negative	0012200000	00000	0000x	No differential diagnosis
76	7	71	Negative	0000000000	00000	0000x	Epilepsy
77	1	56	Negative	0000000000	00000	0000x	Vertigo
78	3	50	Negative	0000000000	00000	0000x	Residual myelitis
79	2	56	Negative	0000000000	00000	0000x	War psychoneurosis
80	6	58	Negative	0000000000	32100	3210x	General arteriosclerosis
81	7	44	Negative	0000000000	00000	0000x	Exophthalmic goiter
82	1	51	Negative	0000000000	00000	0000x	Bladder incontinence
83	2	47	Negative	5544421000	55550	4422x	No differential diagnosis
84	4	77	Negative	0000000000	00000	0000x	Chronic myeloid leucemia
85	2	56	Negative	0000000000	00000	0000x	Question of brain tumor
86	10	38	Negative	0000000000	00000	0000x	General arteriosclerosis
87	2	20	Negative	0000000000	00000	0000x	No differential diagnosis
88	3	129	Negative	1122332100	33330	2322x	Acute frontal sinusitis
89	1	32	Negative	5221100000	22210	2211x	Endocarditis; streptococcus septicemia
90	27	51	Negative	4453210000	45310	2332x	Abscess of scalp
91	14	49	Negative	0000000000	00000	0000x	No differential diagnosis
92	2	43	Negative	0000000000	00000	0000x	Syringomyelia
93	0	167	Negative	0123210000	01220	0122x	Angina pectoris

94	4	49	Negative	1121100000	11220	1221x	Paralysis agitans
95	1	43	Negative	0000000000	00000	0000x	Arteriosclerosis
96	3	31	Negative	0000000000	00000	0000x	External rectus palsy
97	0	56	Negative	5543210000	22330	2233x	General and cerebral arteriosclerosis
98	3	62	Negative	0000000000	00000	0000x	Psychoneurosis
99	0	222	Negative	1223432000	44310	3321x	Brain tumor
100	1	44	Negative	0000000000	00000	0000x	Pernicious anemia
101	8	37	Negative	0000000000	00000	0000x	Typhoid fever
102	0	19	Negative	0000000000	00000	0000x	Carcinoma of the liver
103	1	36	Negative	0000000000	00000	0000x	No differential diagnosis
104	3	34	Negative	0000000000	00000	0000x	No differential diagnosis
105	16	38	Negative	0000000000	00000	0000x	No differential diagnosis
106	0	31	Negative	0000000000	00000	0000x	Cerebellopontine tumor
107	0	45	Negative	0000000000	00000	0000x	No differential diagnosis
108	350	114	Negative	0012222100	12220	1222x	Question of alcoholism
109	3	44	Negative	0000000000	00000	0000x	Phlebitis
110	1	23	Negative	0000000000	00000	0000x	No differential diagnosis
111	0	80	Negative	0000000000	00000	0000x	Diabetes mellitus
112	0	53	Negative	0000000000	00000	0000x	Herpes zoster
113	1	31	Negative	0000000000	00000	0000x	Question of gastric ulcer
114	0	23	Negative	0000000000	00000	0000x	No differential diagnosis
115	3	34	Negative	0000000000	00000	0000x	Question of aortitis
116	1	24	Negative	0000000000	00000	0000x	Hysteria
117	2	67	Negative	0000000000	00000	0000x	Gastric carcinoma
118	6	47	Negative	0122100000	00000	0000x	Pleurisy
119	3	28	Negative	0000000000	00000	0000x	Secondary anemia
120	0	50	Negative	0000000000	01330	0000x	No differential diagnosis

* DENIS, W., and AYER. J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 436.

TABLE X (CONDITIONS OF VARIOUS KINDS—*Continued*)

Case	Cells	Total protein* (in mgms.)	Wassermann reaction	Colloidal reactions			Conditions
				Gold	Benzoin	Mastic	
121	7	55	Negative	0000000000	00000	0000x	Left hemiplegia
122	4	50	Negative	0000000000	01220	0000x	Cerebral hemorrhage
123	3	30	Negative	0000000000	00000	0000x	Peptic ulcer
124	0	50	Negative	0000000000	00000	0000x	Parkinsonian syndrome
125	2	154	Negative	0123211000	12230	0111x	Nephritis
126	0	35	Negative	0000000000	00000	0000x	Question of lead encephalopathy
127	0	65	Negative	0000000000	00000	0000x	Psychoneurosis
128	10	50	Negative	0000000000	00000	0000x	Retention, cause unknown
129	5	73	Negative	0000000000	00000	0000x	Carcinoma of the rectum

* DENIS, W., and AYER, J. B. *Arch. Int. Med.*, Chicago, 1920, xxvi, 436.

TABLE XI
INTERVALS BETWEEN TESTS

First test	Interval	Second test
55210 Benzoin	1 day	55210 Benzoin
5533x Mastic		5543x Mastic
00000 Benzoin	2 days	00000 Benzoin
0000x Mastic		0000x Mastic
55210 Benzoin	3 days	55220 Benzoin
4554x Mastic		4554x Mastic
00000 Benzoin	3 days	00000 Benzoin
0000x Mastic		0000x Mastic
55410 Benzoin	4 days	55410 Benzoin
4333x Mastic		4443x Mastic
14210 Benzoin	5 days	24210 Benzoin
4431x Mastic		4442x Mastic
00000 Benzoin	5 days	00000 Benzoin
0000x Mastic		0000x Mastic
55550 Benzoin	6 days	55550 Benzoin
5544x Mastic		5544x Mastic

TABLE XII
TABLE SUMMARIZING THE COMPARISON OF 400 COLLOIDAL GOLD, BENZOIN AND MASTIC TESTS WITH THE CEREBROSPINAL FLUID

	Number of fluids	Number of cases	Similar reactions in all three tests	Dissimilar reactions
I. Neurosyphilis	185	139	182	3
1. General paresis	11	11	11	0
2. Tabes dorsalis, taboparesis	41	27	41	0
3. Syphilitic meningitis	6	3	5	1
4. Central nervous system syphilis	127	98	125	2
II. Syphilis without central nervous system involvement	44	42	39	5
III. Non-syphilitic, no differential diagnosis	20	20	18	2
IV. Conditions of various kinds	151	136	145	6
	400	334	384	16

Discussion

The following questions submitted to Miss Cockrill before the Commission, together with the answers to them, are here reported verbatim.

Dr. Barker: How does Miss Cockrill account for the discrepancy between the results published in Germany and in France and those found in her own laboratory with regard to the benzoin test? Kafka of Hamburg practically discards the benzoin test as useless; he states that he has tried it repeatedly but that it is very difficult to get a suitable benzoin, that it is not easy to make the readings, that there is a marked inconstancy in the results, and that on the whole it is not a method to be recommended. Does she believe that that criticism is due to purely international difficulties, or to some other causes?

Miss Cockrill: I do suspect that international difficulties may play a large part in these colloidal tests, because the Germans, who presented the colloidal gold and later the mastic test, cannot, or do not, find the benzoin test a very reliable one. On the other hand, the French, who have presented the colloidal benzoin test, find that it is very much more reliable than either the colloidal gold or the mastic.

I think it quite probable that some difficulty in the benzoin test may arise from not using the correct kind of benzoin. The commercial powdered benzoin gives such unstable emulsions that it is not reliable. If, however, the benzoin resin is used in the preparation of the stock solution and if proper care is exercised, I consider, from the 400 examinations that I have performed, that it is a perfectly reliable test, although I feel that the mastic is approximately of the same value. Therefore, ruling out personal feelings, either Germanic or French, it is my opinion that they both are of approximately equal value but that the benzoin is simpler and therefore is the preferable test.

Dr. Jones: I should like to ask whether the benzoin test is of any value. In looking over the transactions of one of the recent Paris meetings, one of the major papers states that the test should be carried out with sixteen tubes. In our own experience we find very few changes in the colloidal gold curve in multiple sclerosis. Therefore, I am raising the question as to whether the benzoin or the colloidal gold test is of greater value.

Miss Cockrill: I believe that the colloidal gold reaction is the preferable test in cases of multiple sclerosis and meningitis. I think the results from the laboratory of the Massachusetts General Hospital show that a rather reliable and constant reaction with the colloidal gold solution in multiple sclerosis is obtained on cases that have been established clinically as multiple sclerosis. I should prefer, from what I know of the colloidal tests, to use the colloidal gold test in cases of multiple sclerosis and meningitis and not the colloidal benzoin. It requires a very elaborate amount of preparation to perform the test with sixteen tubes, and the test becomes as difficult as the colloidal gold reaction. At present the colloidal gold test is better established.

Dr. Spiller: I should like to ask Miss Cockrill in what forms of meningitis she prefers the colloidal gold test.

Miss Cockrill: The colloidal gold test is the preferable colloidal reaction in all non-syphilitic meningitides. I believe that the syphilitic meningitic group may be tested satisfactorily with the colloidal benzoin solution because

the reaction is usually in the lower dilutions and not that supposed to be obtained with the pneumococcus, meningococcus and other pyogenic organisms.

Dr. Spiller: I should also like to ask whether, in the diagnosis of multiple sclerosis (a diagnosis which is often difficult and uncertain without necropsy), the colloidal gold reactions are dependable as distinguishing multiple sclerosis from any other condition.

Miss Cockrill: I consider no one test sufficient to establish any diagnosis, but I believe that the colloidal reaction in multiple sclerosis may be a very valuable diagnostic aid, taken in conjunction with the rest of the picture, both clinical and laboratory.

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Chapter X

THE ELECTRICAL CONDUCTIVITY OF THE SPINAL FLUID

JOHN L. ECKEL, M.D.

THERE has been but a small amount of research work done on the conductivity of the spinal fluid. Polányi[1] made some estimations on fluids from cases of hydrocephalus; Levinson[2] made some studies from a few other conditions, while Crile, Hosmer and Rowland,[3] in their work on conduction of animal tissues, included the spinal fluid from a number of rabbits in their work.

In our investigation we have attempted to obtain fluids from as many pathological conditions of the central nervous system as was possible. A number of these we have been obliged to omit because of inability to obtain the fluids at this time. In one series the number of cases has been rather small, so that we feel we do not wish to draw definite conclusions in that particular series, believing that data from a larger number of cases would be more reliable. However, in the more common diseases of the nervous system our series is fairly large. We are indebted to a large extent to the superintendents and staffs of the Craig Epileptic Colony, Sonyea, N.Y., the Buffalo and Gowanda State Hospitals, and the Buffalo City Hospital for these fluid specimens. These fluids were all collected in sterile tubes, free from electrolytes, and sent to our laboratory immediately after being obtained, and were tested soon after their arrival. In all, we made conductivity tests on over 360 spinal fluids obtained from lumbar puncture.

Technique

For the purpose of making this investigation, the following instruments were used, all being prepared by and tested in the laboratory of the Leeds & Northrup Company of Philadelphia: A typical Wheatstone bridge, made up of a Kohlrausch slide wire and a three-dial resistance coil, with a telephone receiver connected across the ends of the slide wire; a hummer, and a constant temperature bath set at 25°c., and a special conduction cell. This cell is made from glass, the electrodes being platinum, 5/16 inch in diameter. They are connected by a tube 1 inch in length which has an inside diameter of

5/32 inch. In using this for our determinations, it required slightly over 1 c.c. of fluid. In measuring the resistance, we used a series of three cells, all having about the same dimensions, but we very early found there was a slight difference in their resistance measurements. Cell 1 was slightly higher and Cell 3 slightly lower than Cell 2. It was also observed that this difference in Cells 1 and 3 ran parallel, or nearly so, throughout the work. Therefore, we concluded in our summary to use the readings found with Cell 2, as these more nearly represented the average of the three cells.

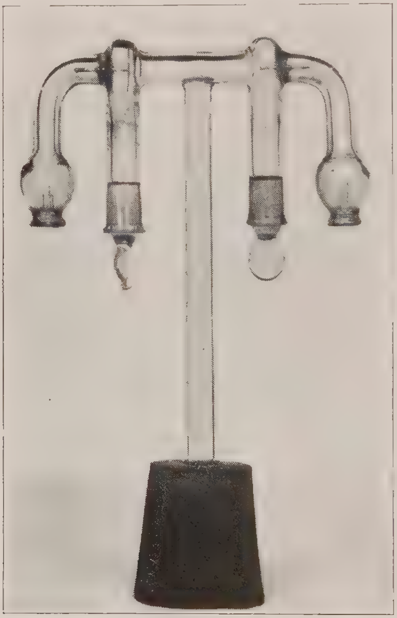

FIG. 2. Cell used in test. Electrodes of platinum 5/16 inch in diameter, 1 inch apart; connecting tube 5/32 inch in diameter.

For the purpose of cleansing these cells for the resistance measurements, we used double distilled water, rinsing them several times, and this was followed by the use of absolute alcohol, which, in turn, was followed by the use of ether.

In making our measurements, several readings were made upon each fluid and the average taken as the final result. All fluids showing any contamination or containing blood were discarded.

After having obtained the resistance of these fluids and having expressed them in ohms, we desired, for the purpose of making our findings clear, to transform them into specific conductance, and to do this we were first obliged to determine our cell constant. For this work we used the technique of H. and E. Parker,[4] in which they used a 0.1 D KCl solution at 25°c. (D = 1 cu.

dec. solution). The specific conductance of this solution they found under those conditions to be .01285.

In the preparation of this 0.1 D KCl solution, 7.479 gms. of fused potassium chloride were weighed in the air and were used to each 1000 gms. of distilled

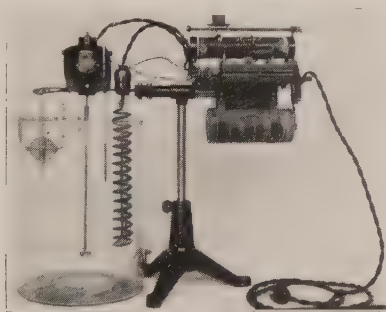

FIG. 3. Constant temperature bath.

water, which was also weighed in the air. By this method no correction for the density of the water was necessary.

The solution having been prepared, the resistance of the distilled water used in the preparation of the solution was then measured at 25°C., and called R_W. After cleansing the cell thoroughly, the KCl solution was placed in it and its resistance measured at 25°C. and called R_S.

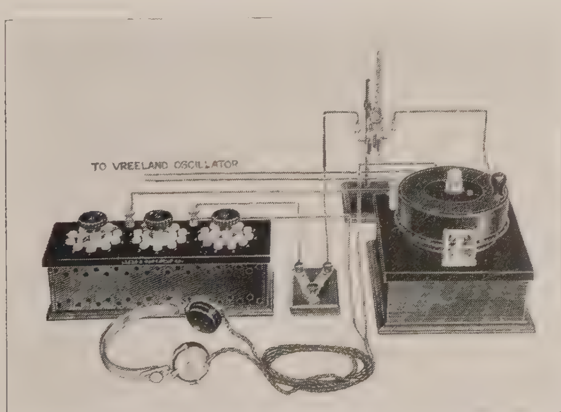

FIG. 4. Wheatstone bridge; three-dial resistance coil and telephone receiver.

The cell constant (C) was found from this equation: $C = 0.01285 \left(0.01285 + \frac{0.01285 \times R_S}{R_W}\right) \times R_S$. The second member in parentheses corrects for the specific conductance of the water; which correction, although found to be almost negligible, has been made in this work.

Having established the cell constant, the specific conductance (L) was found from the following equation: $L = \frac{C}{R}$, in which R is the resistance of the spinal fluid, which we measured at 25°C. in the same cell.

In the preparation of the solutions and in the estimating of the total solids in numerous specimens of spinal fluids, we had the assistance of Dr. George Pucher of the Department of Biochemistry, University of Buffalo, and in the adjusting of our apparatus and the interpretation of our findings we have had the constant assistance of Professors Moore and Cooke of the Department of Physics, University of Buffalo.

The conductivity of the spinal fluid depends upon the salt content of the fluid. These salts are all highly ionized and the conductivity of the cerebrospinal fluid is the relative measure of the total ionized solids present in the fluid. NaCl is present in the largest amount, while potassium, magnesium, iron, phosphorus and other electrolytes are present in smaller quantities. A large number of estimations were made and it was found that the conductivity varied with the salt content of the fluid. The amount of globulin and albumin present in the various fluids, while it does not materially change the conductivity, has some depressing effect.

Table XIII

Specific Conductance, Normal Fluids

Case		Case	
1	.01461	14	.01501
2	.01452	15	.01495
3	.01480	16	.01507
4	.01481	17	.01503
5	.01446	18	.01508
6	.01519	19	.01526
7	.01476	20	.01518
8	.01549	21	.01513
9	.01508	22	.01495
10	.01504	23	.01495
11	.01517	24	.01537
12	.01499	25	.01471
13	.01530	26	.01425

Maximum .01549
Minimum .01425
Average .014967

Gram,[5] in his work on conductivity of the blood serum, found the proteid content to diminish somewhat the resistance, and he

established an equivalent conductance for the proteid content, which, although small, did show a definite resistance of its own. The estimation of the proteid content in each fluid has not been determined in this series, but left for subsequent investigation.

The normal fluids in this series were obtained from cases having other than neurological signs or symptoms, and none of these fluids contained globulin and none showed an abnormal cell count. It will be seen (Table XIII) that there was considerable variation in the conductance of these fluids, which was found to be due to the variation in the salt concentration of the fluid at the time it was obtained. Nearly all the pathological fluids, constituting ten or more in this series, showed an average conductance less than the normal. In a few instances where the series was small, the conductance was slightly higher than the average normal.

TABLE XIV
SPECIFIC CONDUCTANCE, CEREBROSPINAL LUES (EXCLUDING PARESIS AND TABES)

Case		Case		Case	
1	.01508	20	.01522	39	.01478
2	.01509	21	.01492	40	.01514
3	.01472	22	.01574	41	.01486
4	.01423	23	.01495	42	.01455
5	.01474	24	.01488	43	.01475
6	.01508	25	.01510	44	.01457
7	.01474	26	.01478	45	.01475
8	.01508	27	.01473	46	.01470
9	.01472	28	.01478	47	.01475
10	.01474	29	.01441	48	.01453
11	.01503	30	.01495	49	.01463
12	.01507	31	.01473	50	.01537
13	.01503	32	.01478	51	.01476
14	.01503	33	.01514	52	.01482
15	.01476	34	.01495	53	.01482
16	.01476	35	.01453	54	.01421
17	.01501	36	.01460	55	.01478
18	.01501	37	.01460	56	.01460
19	.01449	38	.01524	57	.01570

Maximum .... .01574
Minimum .... .01421
Average .... .014851

Table XIV represents the specific conductance of cerebrospinal lues, exclusive of paresis and tabes. Here again, about the same

TABLE XV
SPECIFIC CONDUCTANCE, TABETIC FLUIDS

Case		Case		Case	
1	.01481	14	.01498	27	.01474
2	.01502	15	.01486	28	.01478
3	.01480	16	.01508	29	.01483
4	.01456	17	.01487	30	.01474
5	.01530	18	.01466	31	.01471
6	.01455	19	.01460	32	.01487
7	.01553	20	.01485	33	.01509
8	.01504	21	.01549	34	.01455
9	.01486	22	.01522	35	.01551
10	.01424	23	.01508	36	.01501
11	.01568	24	.01487	37	.01548
12	.01522	25	.01489	38	.01505
13	.01508	26	.01498	39	.01482

Maximum .01568
Minimum .01424
Average .014956+

TABLE XVI
SPECIFIC CONDUCTANCE, GENERAL PARESIS

Case		Case	
1	.01482	18	.01533
2	.01446	19	.01462
3	.01506	20	.01561
4	.01465	21	.01482
5	.01533	22	.01482
6	.01456	23	.01482
7	.01501	24	.01520
8	.01462	25	.01474
9	.01502	26	.01498
10	.01462	27	.01460
11	.01510	28	.01482
12	.01476	29	.01470
13	.01479	30	.01482
14	.01471	31	.01482
15	.01485	32	.01508
16	.01450	33	.01518
17	.01484		

Maximum .01561
Minimum .01446
Average .014868+

degree of variation is found as in the normal fluids, but the average is slightly lower than that established as the normal. This series contained 57 cases.

In Table xv is represented the conductance in the series of tabes cases, all types. It was found rather difficult to differentiate the degree of activity of the disease in these cases, so they have all been classed under one heading. By this method, no doubt a greater variation in the conductance was found than would have been the case if the fluids had been carefully classified according to the various degrees of activity of the disease. The average conductance is found to be nearly that of the normal fluid.

Table xvii

Specific Conductance, Dementia Praecox, Manic Depressive Psychosis and Involution Melancholia

Dementia praecox				Manic depressive psychosis		Involution melancholia	
Case		Case		Case		Case	
1	.01495	14	.01488	1	.01518	1	.01517
2	.01465	15	.01461	2	.01507	2	.01519
3	.01460	16	.01504	3	.01522	3	.01517
4	.01532	17	.01472	4	.01485	4	.01505
5	.01489	18	.01441	5	.01478	5	.01456
6	.01482	19	.01461	6	.01509	6	.01462
7	.01542	20	.01512	7	.01478	7	.01549
8	.01501	21	.01521	8	.01518	8	.01528
9	.01489	22	.01513	9	.01474	9	.01486
10	.01541	23	.01470	10	.01538	10	.01510
11	.01464	24	.01470	11	.01525		
12	.01514			12	.01508		
13	.01513						
Maximum......... .01542				Maximum.....01538		Maximum....01549	
Minimum...........01441				Minimum.....01474		Minimum 01456	
Average.............014916				Average 015050		Average......0150490	

In Table xvi is shown the conductance of 33 cases of well-developed general paresis. About the same degree of variation is shown as in the previous tables, with the average approximately normal.

In Table xvii is represented a series of cases of dementia praecox, manic depressive psychosis, both phases, and involution melancholia. The praecox cases show the conductance slightly below that of the normal cerebrospinal fluid, while the manic and involu-

tion-melancholia fluids are slightly higher than the average normal. If our series were larger, this average might be reduced and be more nearly that of the normal. However, in all cases where depression was present it was found that the resistance was higher than the average normal.

TABLE XVIII

SPECIFIC CONDUCTANCE OF FLUIDS FROM VARIOUS TYPES OF EPILEPSY

Idiopathic		Hereditary		Alcoholic		Endocrine	
Case		Case		Case		Case	
1	.01551	1	.01484	1	.01469	1	.01511
2	.01473	2	.01494	2	.01494	2	.01513
3	.01487	3	.01469	3	.01486	3	.01508
4	.01473	4	.01483	4	.01493	4	.01501
5	.01470	5	.01477	5	.01513	5	.01515
6	.01427	6	.01498	6	.01473	6	.01499
7	.01480	7	.01490			7	.01527
8	.01478	8	.01491			8	.01508
9	.01477	9	.01482			9	.01523
10	.01423	10	.01476			10	.01518
11	.01455	11	.01490				
12	.01481	12	.01470				
		13	.01477				
		14	.01497				
Maximum	.01551	Maximum	.01498	Maximum	.01513	Maximum	.01527
Minimum	.01423	Minimum	.01469	Minimum	.01469	Minimum	.01499
Average	.014895	Average	.01483+	Average	.014880	Average	.015123

In Tables XVIII and XVIII-A are represented the conductance of the fluids from the various types of epilepsy. There were 100 fluids in this series. All but 30 of these were classified as to type. All types, except the endocrine and the traumatic, showed lower conductance than normal, while the endocrine and the traumatic showed a slight increase over the established normal.

Table XIX represents the results in a series of cases of hemiplegia and myelitis, containing all types except those caused by syphilis. The cases of hemiplegia were of several weeks' standing. In both of these conditions the average conductance was below the normal, which was particularly noticeable in those due to myelitis.

TABLE XVIII-A

SPECIFIC CONDUCTANCE, EPILEPSY

Traumatic				Unclassified types			
Case		Case		Case		Case	
1	.01532	15	.01504	1	.01498	16	.01484
2	.01488	16	.01507	2	.01488	17	.01486
3	.01477	17	.01527	3	.01480	18	.01493
4	.01494	18	.01575	4	.01480	19	.01486
5	.01496	19	.01532	5	.01494	20	.01484
6	.01490	20	.01500	6	.01487	21	.01519
7	.01488	21	.01506	7	.01478	22	.01521
8	.01506	22	.01542	8	.01487	23	.01521
9	.01509	23	.01528	9	.01490	24	.01512
10	.01498	24	.01551	10	.01473	25	.01509
11	.01506	25	.01534	11	.01506	26	.01486
12	.01507	26	.01519	12	.01501	27	.01493
13	.01505	27	.01523	13	.01477	28	.01507
14	.01525	28	.01534	14	.01490	29	.01516
				15	.01484	30	.01519
Maximum.................01575				Maximum.................01521			
Minimum.................01477				Minimum.................01473			
Average.................015143+				Average.................0149496			

TABLE XIX

Specific Conductance, Hemiplegia		Specific Conductance, Myelitis, All Types	
Case		Case	
1	.01480	1	.01468
2	.01498	2	.01456
3	.01517	3	.01446
4	.01488	4	.01512
5	.01478	5	.01447
6	.01549	6	.01426
7	.01458	7	.01489
8	.01457	8	.01436
		9	.01502
Maximum.................01549		Maximum................. 01512	
Minimum.................01457		Minimum................. 01426	
Average.................014906+		Average................. 014646	

In Table xx is represented the resistance in a large number of conditions, in none of which was our series large enough to warrant definite conclusions. While some are above the normal, it will be observed that they all approximate the average normal.

TABLE XX

SPECIFIC CONDUCTANCE, VARIOUS CONDITIONS OF NERVOUS SYSTEM

Cerebral arterio-sclerosis		Neurasthenia		Lateral sclerosis		Brain tumor	
Case		Case		Case		Case	
1	.01513	1	.01491	1	.01478	1	.01528
2	.01544	2	.01461			2	.01478
3	.01514					3	.01558
Average .015236+		Average .014760				Average .015213	
Senile dementia		Paranoid condition		Hydrocephalus		Post-meningeal hemorrhage	
1	.01444	1	.01513	1	.01452	1	.01442
2	.01503			2	.01516	2	.01364
3	.01514						
Average .014870				Average .014840		Average .014030	
Alcoholic depression		Delirium		Psychoses and mental depression		Multiple sclerosis	
1	.01547	1	.01530	1	.01508	1	.01486
2	.01510			2	.01522	2	.01447
Average .015285				Average .01515		Average .014665	
Meningo-encephalitis, old							
1	.01465						

Table xxi represents the specific conductance of conditions wherein there is present a meningeal reaction as well as a constitutional reaction, and this table gives the most striking results. In poliomyelitis the average conductance is considerably less than

the normal, while in the epidemic type of meningitis it is still lower. It is decidedly decreased in the tubercular form of meningitis. In the tubercular type the chlorides in the fluid are markedly decreased and the conductance bears a distinct relation to this decrease of the chloride content in the fluid.

TABLE XXI

SPECIFIC CONDUCTANCE, ACUTE INFECTIONS INVOLVING MENINGES

Poliomyelitis		Epidemic meningitis		Tuberculous meningitis	
Case		Case		Case	
1	.01426	1	.01439	1	.01268
2	.01478	2	.01382	2	.01226
3	.01471	3	.01430	3	.01323
		4	.01390	4	.01317
				5	.01374
				6	.01371
				7	.01374
				8	.01313
				9	.01345
				10	.01323
Average .014583		Average .0141025		Average .013234	

Normal:
- Maximum .... .01549
- Minimum .... .01425
- Average .... .014967

SUMMARY AND CONCLUSIONS

Conductivity tests were made on over 360 spinal fluids obtained from both normal and abnormal conditions of the central nervous system.

All tests were made with a constant temperature bath at 25°C.

The cell used in these measurements was of glass, with platinum electrodes, 5/16 inch in diameter, connected by a tube 1 inch in length, having a diameter of 5/32 inch.

It was found that the conductivity depends on the total ionized solids of the fluid, which is composed chiefly of sodium chloride and other electrolytes.

The proteid content of the fluid retards slightly the conductance, but in this investigation no correction was made for this difference, that being left for future work.

All results have been expressed in specific conductance, for which a 0.1 D KCl solution at 25°c. was used, as per the technique of H. and E. Parker (D = 1 cu. dec. of fluid).

Table XXII

Summary of Specific Conductance, All Cases

Type of condition	Cases	Maximum	Minimum	Average for series
Normal	26	.01549	.01425	.014967
Cerebrospinal lues	57	.01574	.01421	.014851
Tabes, all types	39	.01568	.01424	.014956+
General paresis	33	.01561	.01446	.014868+
Manic depressive psychosis	12	.01538	.01474	.015050
Dementia praecox	24	.01542	.01441	.014916
Involution melancholia	10	.01549	.01456	.0150490
Epilepsy:				
Idiopathic	12	.01551	.01423	.014895
Hereditary	14	.01498	.01469	.01483+
Alcoholic	6	.01513	.01469	.014880
Endocrine	10	.01527	.01499	.015123
Traumatic	28	.01575	.01477	.015143+
Unclassified types	30	.01521	.01473	.0149496
Hemiplegia	8	.01549	.01457	.014906+
Myelitis	9	.01512	.01426	.014646
Cerebral arteriosclerosis	3	.01544	.01513	.015236+
Senile dementia	3	.01514	.01444	.014870
Alcoholic depression	2	.01547	.01510	.015285
Neurasthenia	2	.01491	.01461	.014760
Multiple sclerosis	2	.01486	.01447	.014665
Hydrocephalus	2	.01516	.01452	.014840
Psychoses and mental depression	2	.01522	.01508	.01515
Brain tumor	3	.01558	.01478	.015213
Meningoencephalitis, old	1	.01465	.01465	.01465
Lateral sclerosis	1	.01478	.01478	.01478
Delirium	1	.01530	.01530	.01530
Paranoid condition	1	.01513	.01513	.01513
Post-meningeal hemorrhage	2	.01442	.01364	.014030
Epidemic meningitis	4	.01439	.01382	.0141025
Poliomyelitis	3	.01478	.01426	.014583
Tuberculous meningitis	10	.01374	.01226	.013234

In comparing the results found in the various conditions of the central nervous system, it is rather striking how closely these fluids compare with the average normal, both in the maximum and minimum and the average resistance measurements. The only striking exception to this is found in those conditions showing

marked meningeal reaction, which is most marked in the tubercular form of meningitis, and this is explained by the very low chloride content of the fluid in that condition.

Discussion

The following questions submitted to Dr. Eckel before the Commission, together with the answers to them, are here reported verbatim.

Dr. Patterson: What relation, if any, does Dr. Eckel find between the electrical conductivity and the hydrogen-ion concentration of the spinal fluid?

Dr. Eckel: We did not go into that phase of the investigation.

Dr. Barker: Since the results of this test seem to run closely parallel to those obtained by determination of the sodium chloride content in the cerebrospinal fluid, I should like to ask which determination, provided that the apparatus is set up and working satisfactorily, would be the easier and quicker, the ordinary sodium chloride determination or this electrical conductivity determination?

Dr. Eckel: If the apparatus is set up in working order and the thermostat is working, I think the electrical conductivity estimation is simpler. When the apparatus is set up it works very smoothly and a reading can be made in about two minutes.

Dr. Fremont-Smith: What precautions, if any, are necessary in the determination of the electrical conductivity, to prevent the loss of CO_2 from the spinal fluid after withdrawal? Would such loss of CO_2 affect the electrical conductivity?

Dr. Eckel: While we did not make specific tests for that, we did take quite a series of fluids, tested them within ten minutes after obtaining the fluid and made subsequent examinations at definite intervals. With this method we found that in tests extending over a period of four or five days, if the fluid was kept sterile, there was no difference in the electrical conductivity.

Dr. Sachs: This is an extremely interesting presentation, but I would like to ask Dr. Eckel whether he believes that the further determination of this electrical conductivity may have any bearing upon the understanding of these various pathological processes.

Dr. Eckel: I do not think so. I feel that the total determination of the solids present would in the end be much easier, because it is not possible to have this apparatus in every laboratory and because a special operator would be required to make the investigations. The chemical method would be simpler.

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Section III

PRESSURE STUDIES ON THE CEREBROSPINAL FLUID

Section III

PRESSURE STUDIES ON THE CEREBRO-SPINAL FLUID

Chapter XI

CEREBROSPINAL FLUID PRESSURE FROM THE CLINICAL POINT OF VIEW*

JAMES B. AYER, M.D.

IN every diagnostic lumbar puncture a manometer should be used. This is not only my opinion, but must be that of any one seeking all the information that can be gained from spinal fluid examination. It is true that great variations occur within what we call the limits of normal pressure, and that *normal* varies greatly with different conditions: but it is also true that we can recognize definitely pathological pressures. Therefore, I reiterate that the analysis of the study of any spinal fluid is inadequate if the pressure findings have been neglected.

In advocating pressure studies in diagnostic punctures I refer not only to the reading of the initial pressure, but also to subsequent pressure readings following certain procedures which give us a conception of the amount of fluid present in the cerebrospinal reservoirs, and also evidence of block in the fluid pathways. Moreover, while much may be learned from pressure studies on the lumbar fluid, in selected cases pressure estimations should be carried out synchronously in different loci of the ventriculo-subarachnoid spaces.

It is not stating too much to say that in some cases the pressure studies, so frequently neglected, constitute the most important part of the spinal fluid examination.

Apparatus

Three types of manometer are in use, and each has its advocates: the mercury manometer, the tambour type of recorder and the aqueous manometer. My experience relates solely to the latter type. Any glass tube graduated in centimeters will suffice; the inside diameter should not be greater than 2 mm. or less than 1 mm. For convenience, two lengths of 350 mm.

* From the Department of Neurology, Massachusetts General Hospital.

each are recommended. Such a manometer is easily carried, thoroughly sterilizable, convenient to use and replaceable upon breakage without great expense.

It is advisable that a three-way stopcock be interposed between the needle and the manometer for the withdrawal of fluid without necessitating the disconnection of the manometer. The accuracy of the readings in such a manometer, when the height of the spinal fluid column is read, has been justly called into question; certainly it is not accurate, but it is nearly enough accurate for clinical purposes. In such a manometer as described, not over five drops of fluid are lost in connecting the apparatus when a normal pressure is present: a negligible loss from a fluid reservoir of approximately 150 c.c. I have on many occasions checked the reading when spinal fluid was allowed to run up the tube, by a previous reading when the manometer was first filled with physiological salt solution to balance exactly the spinal fluid pressure; the readings by the two methods seldom differing by more than one centimeter.

The mercury manometer has one advantage: it is less cumbersome than the aqueous manometer in measuring very high pressures. If the U-tube type is used, it is possible also to measure negative pressures, which are of little clinical value but useful in physiological studies. In estimating low pressures, the readings are so small as to render slight variations almost illegible. Most important of all, however, the inertia of the mercury dampens the oscillations occasioned by the pulse and respiration, variations to which we have attributed a certain value in using the aqueous manometer.

The tambour type of manometer such as that of Claude and that of Ayala, is evidently employed by a number of physicians on the Continent. With these instruments the writer has no acquaintance. Most pressure readings in the literature of this country and abroad are expressed in millimeters of spinal fluid. Mercury manometers have found favor especially with surgeons who are accustomed to meet with high pressures. In reporting cases it is obvious that the writer should specify the type of instrument used; and whatever the type of manometer chosen, it should be used consistently in order to obtain comparative results.

Estimation of the pressure by counting the drops per unit of time cannot be too severely condemned. Many times have I seen fluid come slowly from the needle, only to mount to pathological heights in the manometer; by the "drop method" such a fluid would have been said to have shown a low pressure.

Conversely, if the fluid spurts from the needle, it is said to be under high pressure. This may be the case, but it is possible that the spurting was due to some movement of the patient or other mechanical factor which is known to cause a transitory increase in pressure, factors readily detected in the manometer. It is therefore apparent that a false conception is gained as to both high and low pressures by observation of the rate of flow.

Normal Pressure

It has been said that "normal pressure may be almost anything." Certainly a wide range of normality must be admitted. As this variation is as much a matter of opinion as of statistics, I should

place the normal cerebrospinal fluid pressure between 100 and 200 mm. of water. It will be found that the majority of initial pressure readings falls within these figures. Pressures between 200 and 250 mm. are suspiciously high, and 250 to 300 mm. are in my opinion definitely abnormal. Pressures over 300 mm. are probably always to be explained on a basis of intracranial pathology. Weigeldt[1] gives substantially the same limits: he states that the normal level ranges between 150 and 170 mm. He quotes Becker as giving an average normal of 162 mm., and von Bottner, of 40 to 130 mm. Weigeldt states that pressures over 300 mm. are always pathological, while Dreyfus and Becker (quoted by Pappenheim[2]) give 200 and 220 mm. as the upper limit of normal.

While there is more or less agreement as to pathological readings, nobody has set any low limit to normal. It is not infrequent to find a pressure well below 100 mm. which cannot be explained on a pathological basis.

Our figures are for patients lying on the side, with the axis of the spine horizontal and the head in alignment. In this position the pressures in the cisterna magna and lateral ventricle are the same as in the lumbar sac; i.e., the heights of the fluid columns are at the same level so far as the eye can tell or a spirit level can detect. Similarity of pressures in these different loci is not agreed to by all; Weigeldt believes that the ventricular pressure is normally a very little higher than that in the subarachnoid space; and Riser[3] states that in the strictly horizontal position the ventricular pressure is zero.

It is possible that the discrepancy between our findings and those of the French depends upon the method of puncturing the ventricle. They use a needle which exactly fits the opening in the skull, while we have used a small trephine opening. In our cases the brain is certainly open to atmospheric pressure influences; whereas it is likely that this is not the case with the French method. However, I am told that Purves Stewart, employing an instrument similar to that used by Riser, obtains positive ventricular pressures equal to the lumbar pressures.

In the sitting posture, the lumbar pressure is approximately doubled, the height of pressure depending upon the length of the trunk, while at the cisterna magna the pressure is below zero; i.e., it is a negative pressure. Similarly, the ventricular pressure is negative, a fact which can readily be checked by palpation of the normal infant's fontanelle.

Solomon has observed the fluid pressures in the ventricle and lumbar sac, and I have examined the pressures in the cisterna magna and lumbar sac during changes in position, with the result that with the head raised or feet raised the pressures always remained on the same horizontal plane, even when negative pressure was measured in a U-tube.

In pressure determinations there are a number of pitfalls. Holding the breath, coughing, sneezing, grunting, but especially a cramped position all tend to elevate the pressure to a considerable extent. Occasionally faintness overtakes a patient during lumbar puncture and this is accompanied by an immediate drop in pressure. Solomon, Thompson and Pfeiffer[4] have made a study of these physiological influences on pressure and conclude that pressure readings should not be made until ten minutes after the insertion of the needle, in order to allow for the cessation of these effects on the cerebrospinal fluid pressure. I am of the opinion that in most subjects, if the puncture has been painlessly performed and *the patient not held in a cramped position*, the reading may be made immediately without undue inaccuracy.

Among the number of physiological acts which lead to variation in pressure is one which has found a place as an important diagnostic aid. It was long ago noted that constriction of the neck caused an increase in spinal fluid pressure.[5] But it was Queckenstedt[6] who first analyzed the significance of jugular compression in causing increased intracranial pressure which could be detected immediately by an increase in the fluid pressure in the lumbar sac. Queckenstedt's sign is now employed as a routine procedure in every diagnostic lumbar puncture as an indication of the patency of the spinal subarachnoid space. A failure of the pressure to rise usually denotes a block in the spinal subarachnoid space, but there are exceptions, as noted below. The importance of this sign of jugular compression is so great that two personally observed errors in carrying out this test should be stressed. In a few cases in which the pressure was low, I have failed to obtain the expected rise. After injecting salt solution to increase the intradural tension, a prompt rise was seen on repeating the jugular compression. Conversely, I have seen a normal Queckenstedt sign in the presence of cord compression when the test was incorrectly done, due to the fact that the hand which compressed the jugular veins also temporarily shut off the breathing and produced a cough, factors

which we know will elevate the fluid pressure below high thoracic and cervical tumors.

The variation in spinal fluid pressure coincident with different blood pressures has been the subject of study by a number of of workers. The conclusions reached by Block and Oppenheimer[7] fairly summarize this situation: "No individual parallelism exists between intraspinal pressure, arterial pressure and ocular tension," but "on an average, a high pressure of one type is associated with a high pressure of the other types; the same is true of low pressure." However, Bailliart, Magniel and Saragea,[8] by using a special technique for measuring pressures in the retinal arteries, believe that cerebral arterial hypertension, as estimated in the retinal arteries, is accompanied by an increased spinal fluid pressure.

No great difference in pressure at different ages is recognized, except that, as noted in the previous paragraph, the higher the blood pressure, the higher, as a rule, will be the spinal fluid pressure. It should be noted here that the pressure readings in infants and young children are notoriously unreliable, in that the conditions required for dependable readings, namely, complete physical and emotional relaxation, are most difficult to attain.

Pressure readings in patients under general anesthetics usually run higher than normal, due to cerebral venous congestion, and are, therefore, unreliable as to their significance. Such readings, due to a disturbed physiology, mark a transition in the readings between normal and pathological states.

Pathological Increase in Pressure

An analysis of the possible factors concerned with pressure regulation of the cerebrospinal fluid may be stated as follows:

1. The elasticity of the dura mater
2. Intracranial arterial pressure
3. Intracranial venous pressure
4. The "secretion pressure" of the cerebrospinal fluid
5. The rate of absorption of the fluid
6. Brain bulk, or the amount of solid substance within the cranium
7. Hydrostatic pressure, provided the patient is in any position other than the horizontal.

Analysis of the pathological conditions causing high cerebrospinal fluid pressures will usually indicate that abnormality of one of these criteria of pressure is of prime importance, but that

one or more of the other factors are also operative. Thus, in acute meningitis, in which condition we find the highest pressures, we are dealing with an excess of intracranial contents, i.e., the products of inflammation, but also with excess production of cerebrospinal fluid and diminished absorption.

Pathological conditions causing the highest pressures, even up to 1000 mm. of water, are acute meningitis, brain tumors, hydrocephalus and hemorrhage, both cerebral and meningeal. Among the diseases in which somewhat lower readings are usually found, seldom exceeding 500 mm., are tuberculous meningitis, aseptic meningitis, uremia, polycythemia, cerebral thrombosis and brain abscess.

While the above groups are reasonably made, it must be noted that no hard and fast grouping is possible. When it is admitted that any of the diseases occurring in either group may present normal pressure readings, it is obvious that statistical representation would be unreliable.

Significance of Low Pressure

It has already been stated that the lower limit of normal pressure is not established. It is an occasional experience in apparently healthy individuals to find the pressure so low that fluid will not flow from the needle until the hydrostatic pressure is brought into play by sitting the patient up, or until means have been employed artificially to increase intracranial pressure.

Among pathological states it has been found that in fainting and in shock the pressure is frequently very low. In patients with headache following lumbar puncture the pressure is usually low, much lower than on the previous tap. Also, in patients with long-standing degenerative disease of the central nervous system, where there is an actual diminution of neural substance, the pressure is frequently low.

Special Studies on Pressure Variations

As was stated at the outset, our interest is not confined to the initial pressure readings, important as these may be in certain pathological conditions. We are interested also in pressure studies carried out under known physiological conditions, and in relative pressures at different loci. Among these studies may be mentioned the following:

1. *Pressure Readings Following the Administration of Hypertonic and Hypotonic Saline Solutions.* Since the demonstration by Weed and McKibben[9] of the physiological effect of the administration of different concentrations of salt solutions, therapeutic application of this principle has been made. Their experimental findings have been paralleled in man with regard to a progressive drop in pressure after the administration of concentrated solutions in cases of brain tumor, meningitis, cerebral hemorrhage, general paresis, epilepsy and other diseases (see references 10, 11, 12, 13, 14, 15).

In patients presenting low pressures an elevation of the pressure subsequent to the intravenous injection of distilled water has been demonstrated, with concomitant improvement in conditions of shock, or of hypotension headache.[16] (For a detailed description of pressure variation as a result of saline injections, see the papers of Dr. Aycock and Dr. Howe.)

2. *Traumatic intracranial hemorrhage and cerebral concussion* have been systematically studied from the spinal fluid pressure standpoint, and a number of workers testify to the value of the method as an all-important guide in the reduction of intracranial pressure.[17]

By the slow withdrawal of fluid, thus reducing the pressure to normal or nearly normal levels, it has been found possible to postpone operation beyond the period of shock and in some cases even to dispense with operation altogether. But it is the pressure and not the quantity of fluid withdrawn which forms the guide in such cases.

3. *Ayala's Index.* Repeated pressure readings after withdrawal of known amounts of fluid unquestionably yield information as to the amount of fluid in the ventriculo-subarachnoid system. The writer has for several years made it a custom to take three readings, the initial pressure, the reading after withdrawal of 5 c.c. and a third reading after taking 10 c.c. of fluid. After the withdrawal of the first 5 c.c., the pressure usually falls about 30 mm.; and after the second 5 c.c., about 20 mm. While the normal variation is very marked, there can be little doubt but that a drop of only 10 mm. or 20 mm. after withdrawal of 10 c.c. of fluid is highly suggestive of a large reservoir, as in hydrocephalus or serous meningitis; also that an excessive drop is indicative of a small reservoir, as in loculation of the fluid below a cord tumor.

Ayala[18] has reduced his figures to a common denominator and expresses the result in an equation: $\frac{Q \times F}{I} = qr$; i.e.,

$$\frac{\text{Quantity taken} \times \text{Final pressure}}{\text{Initial pressure}} = \text{rachidian quotient.}$$

Balduzzi,[19] using this index in brain tumor and serous meningitis, claims that a quotient less than 5 speaks for the presence of a tumor, and that a quotient over 7 indicates the existence of a serous meningitis.

Figures of the writer reduced to an index show much greater variation in these two diseases. Still, it must be admitted that a rough estimate of the content of the cerebrospinal fluid reservoirs is obtained by this method.

4. *Combined Readings.* Pressure determinations carried out synchronously, in two or more loci, under a variety of conditions, have given us conceptions of the cerebral circulation which previously have been a matter of speculation. I refer especially to the fact, already mentioned, that in the horizontal position the normal cerebral fluid pressure is positive, while in the upright position it is negative (with zero pressure located somewhere below the cisterna magna). Under pathological conditions leading to increased intracranial pressure, this is not the case, the fluid pressure everywhere being elevated.

Combined readings have been shown to be of reliable diagnostic value in the demonstration of the existence of a block in the cerebrospinal fluid pathways. Block in three different loci of the ventriculo-subarachnoid spaces has been demonstrated by this method of double puncture, the location of the punctures depending upon the site of the lesion: cisternal-lumbar punctures for spinal cord lesions,[20] double lumbar punctures for cauda equina lesions[21] and ventriculo-lumbar punctures for cerebellar fossa pathology.[22]

The criteria upon which block is demonstrated are the same in all three types of procedure; namely, the determination that pressure artificially elevated or depressed in one manometer is not transmitted to the other. The agent found to be of greatest value in raising the pressure is compression of the jugular veins; for reduction of pressure, simple withdrawal of fluid.

While complete block is a most striking and reliable sign, incomplete block, in which partial communication may be shown by tardy equalization of pressure in the two manometers, is of

great significance, especially when correlated with a varying protein content of the two fluids.

5. *Dynamic Studies in the Diagnosis of Lateral Sinus Thrombosis.* Evidence is accumulating that the Queckenstedt test is of value in the determination of the patency of the lateral sinuses, and, in the case of thrombosis, in indicating which side is obstructed.[23] In complete sinus thrombosis the lumbar pressure is found to be unaffected by jugular compression on the side of the affected sinus or to rise only a little; whereas jugular compression on the unaffected side produces an excessive rise, commensurate with the normal reaction observed when both jugular veins are compressed synchronously.

The significance of an unequal rise, upon compression of the jugular veins separately, is not yet certain. The fact that the sinuses are occasionally of different caliber, and that the compression cannot be exactly the same on the two sides makes it unreasonable to place too great dependence upon such findings as indicative of a mural thrombosis.

Conclusions

An attempt has been made to indicate the technique and value of a manometric study of the cerebrospinal fluid. The value of pressure determination is amply demonstrable to any one who systematically carries out the simple procedures suggested in connection with diagnostic lumbar puncture.

While initial pressure readings are often of real diagnostic value, increasing interest attaches to the behavior of fluid pressure under the influence of certain physiological acts, especially when pressure observations include more than one portion of the ventriculo-subarachnoid system. In this manner, pressure studies form the basis of an understanding of the dynamic physiology of the fluid circulation.

Discussion

The following questions submitted to Dr. Ayer before the Commission, together with the answers to them, are here reported verbatim.

Dr. Spiller: I have seen, in consultation, paralysis from puncturing directly over the conus, presumably from injury of the spinal cord. I would therefore ask Dr. Ayer whether he can recommend puncturing over the conus at the level of the first lumbar vertebra as a procedure which is of no danger?

Dr. Ayer: I should certainly not recommend it as a routine procedure. I have done it about twelve times, in cases where I wanted to get above and

below a low tumor. I have had only clear fluids, and I have never seen a hemorrhage or clinical trouble from this puncture.

Dr. Spiller: I should like to ask whether Dr. Ayer can make any difference in diagnostic importance between the protein content in a case of early spinal tumor where the block is just beginning, and the protein content in the lumbar fluid from a case of cerebral tumor. I think he said that the protein content was increased with cerebral tumor.

Dr. Ayer: The protein content alone will certainly not tell you. The manometric studies are of prime importance, but we must admit that subtentorial tumors give evidence of block as well as cord tumors. It is for this reason that combined ventricular-lumbar puncture with manometric studies is indicated in questionable brain tumor.

Dr. Spiller: I should also like to ask how often Dr. Ayer would recommend ventricular puncture in acute meningitis in the early stage, or would he wait until he had evidence of block?

Dr. Ayer: From evidence at hand to date, I believe we are hardly justified in performing ventricular puncture early in meningitis, except as it is understood that we are doing it for a fuller understanding of the particular patient in question. While I do not think we are entitled to promise much from early ventricular puncture, I believe that only by studying fluid at different loci in the ventricular-spinal pathways in early infections, shall we obtain newer conceptions of meningitis.

Dr. Spiller: Does Dr. Ayer expect any better results with the serum in pneumococcus meningitis?

Dr. Ayer: I should expect nothing from any present-day treatment in pneumococcus meningitis. That would be my chief argument in recommending something different, and a logical different type of therapy is multilocular puncture. In the group of meningococcus infections Howell and Cohen (*Am. J. Dis. Child.*, Chicago, 1922, xxiv, 427) showed that serum used early by the ventricular route gave better results than in patients treated purely by the lumbar route.

Dr. Meyer: I should like to ask Dr. Ayer whether he has been able to get any help from the autopsy services in connection with the meningitis problem. For years I have found that in some cases I was able to get evidence, post mortem, of the existence of an inflammatory process in the ventricles, and in others absolutely no such evidence. We evidently deal with types worth differentiating. I cannot help but feel that if the autopsy service were informed of the problem and the matter were insisted upon, we would be able to get very satisfactory and helpful data in this direction.

I should like to ask Dr. Ayer whether he has been able to get such cooperation.

Dr. Ayer: I have been closely associated with the Pathological Department at the Massachusetts General Hospital for a number of years and have obtained a certain amount of cooperation in the study of meningitis, but it is difficult for a general pathologist to grasp the problems of neuropathology.

As Dr. Meyer has observed, some brains appear to show clean ventricles with septic meningitis, yet only this week I saw a case of meningitis of forty-eight hours' duration in which the ventricles showed more evidence of infection than did the subarachnoid space.

Dr. Sachs: I should like to ask Dr. Ayer whether he would find it practical in a given case to make use of the protein determination for the localization of spinal cord tumor, and whether he would consider that method more practical, for instance, than the injection of lipiodol, which has been used?

Dr. Ayer: If I may take one minute I can give you our method of handling a cord tumor suspect from the spinal fluid diagnostic point of view. We place the patient on his side, prepared to perform both lumbar and cisternal punctures. With a lumbar manometer in place, we perform the Queckenstedt test and we examine the first fluid that comes for protein by a naked-eye estimation. If we find that the fluid is xanthochromic and contains a large amount of protein and also that jugular compression shows a complete block, we go no further. If, however, the fluid is clear and colorless, presents only a little increase in protein and the Queckenstedt sign is doubtful, we immediately puncture the cisterna magna. We can then obtain much more accurate information as to block than from the lumbar fluid alone. Another possibility is that we may have a patient in whom we can demonstrate block but cannot be certain of our level. In this case, we inject lipiodol into the cisterna.

Speaking roughly, we employ cistern puncture in combination with lumbar puncture in about 50 per cent of our cases. We use lipiodol in about 25 per cent. That leaves a considerable number of patients in whom lumbar puncture alone is considered sufficient to confirm the diagnosis of subarachnoid block.

Dr. Patterson: What cell count does Dr. Ayer find in brain or cord tumor?

Dr. Ayer: In uncomplicated cases I believe it is unusual to find an increased number of cells in the fluid obtained in cases of brain tumor. A small number, perhaps ten to twenty cells, I believe may occur from irritation about the tumor.

Dr. Spiller: Does it not depend somewhat upon the character of the tumor? Might one not expect to find cell increase in the spinal fluid in a case with brain tumor of a loose, friable, highly cellular character?

Dr. Ayer: I have not enough data to say which type of tumor will give cell increase. Until recently, before we adopted the method of combined ventricular and lumbar puncture, we were very chary about examining the fluid in cases of brain tumor, so my fluids from cases of brain tumor are relatively few.

Dr. Elsberg: Has Dr. Ayer seen any distinct differences between extradural tumors, both as regards protein and cells?

Dr. Ayer: I have not found evidence in the fluid which helps in determining whether a tumor be extradural or intradural. I do believe that tumors which lie low in the spine give us the stronger protein reactions and also that tumors which cause compression rapidly give us great excess of protein.

Dr. Spiller: I am familiar with the mercury manometer reading and not with the aqueous. I shall have to employ the terms, therefore, used with the mercury manometer. Would Dr. Stookey or Dr. Ayer recommend the removal of the fluid at all where the pressure was high, 18 to 25 millimeters of pressure? Do they consider it safe to take away even a small amount of fluid? In cases of brain tumor, we have felt that if the pressure is not very high, we may with safety take away 4 to 5 c.c. of cerebrospinal fluid, watching the fall of the pressure very carefully; but where the pressure is very high, it is not advisable to take away any. Does Dr. Ayer think it is dangerous to take away any fluid in the presence of moderate or high pressure?

Dr. Ayer: I think the danger comes solely in subtentorial tumors. My feeling is that in these cases it is dangerous even to puncture the dura without taking fluid, because with high pressure the hole made in the dura is sufficient to allow fluid to seep into the epidural space, as indeed we know that it does normally. I have seen such seepage in animals in which India ink was injected.

If no tumor is present, the release of spinal fluid is of value. This is seen not only in serous meningitis but in certain hemorrhagic and traumatic states. I think it is questionable, however, whether lumbar puncture should be performed where the presence of tumor is highly probable.

Dr. Spiller: That brings up another question. There are certain cases, as Dr. Ayer himself has said, where a definite clinical diagnosis is absolutely impossible; the symptoms are not sufficient to justify the diagnosis of brain tumor. I have seen some cases where the diagnosis was doubtful but where there was a considerable choked disc of 4 or 5 diopters, that have had lumbar puncture performed and as much as 5 c.c. of cerebrospinal fluid removed. I reported some cases with Dr. de Schweinitz some years ago, in which that method caused a decrease of 1 diopter of swelling within twenty-four hours, and those patients got well; they did not have a brain tumor. I should like to ask Dr. Ayer, therefore, if he has found that the removal of a small amount of fluid, two or three times, lessens materially the pressure of the cerebrospinal fluid.

Dr. Ayer: I think that in serous meningitis, meningism and in cases with lacerated brain, fluid pressure may be reduced with benefit.

Dr. Spiller: When you were in doubt, how would you make sure?

Dr. Ayer: I have often been in doubt and usually have refrained from puncturing in such cases. I admit that I have occasionally done it and taken a chance, by using a needle of very small bore with the hope that if release of fluid is harmful, the mechanism by which it works will take considerable time.

Dr. Spiller: What would you recommend?

Dr. Ayer: I should recommend combined ventricular and lumbar puncture in cases of probable brain tumor. Diagnostic work by this combined puncture will be reported this afternoon.

Dr. Strauss: Has Dr. Ayer, in his experience, when he has used a manometer and done a lumber puncture, ever had a sudden death?

Dr. Ayer: No. There was a case on the Neurological Service at the Massachusetts General Hospital in 1912, a patient who died of respiratory paralysis the day following a lumbar puncture. From the presence of a flattened medulla and an indentation of the cerebellar hemispheres, I believe that the withdrawal of fluid played a major part in the immediate death of this patient.

Dr. Strauss: Is it not true that when there is a manometer attached to the needle, the pressure within the cranial cavity remains to all practical purposes the same as before the puncture? The intracranial pressure is not changed to any extent, is it?

Dr. Ayer: If there is no block, I think you are reducing the intracranial pressure somewhat.

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Chapter XII

COMBINED VENTRICULAR AND LUMBAR PUNCTURE IN THE DIAGNOSIS OF BRAIN TUMOR*

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IN certain patients complete neurological study is not possible. In others the result of examination may still leave in doubt the localization of an intracranial tumor. In such cases we suggest the use of combined ventricular and lumbar puncture as an aid to localization.[1]

Cerebrospinal syphilis may cause papilledema and in other ways simulate brain tumor; yet syphilis cannot be excluded without lumbar puncture, since the Wassermann reaction is usually negative in the ventricular fluid, even in cases of active neurosyphilis,[2,3,4] and may also be negative in the blood.

We have performed combined ventricular and lumbar puncture in twenty-two instances on twenty-one patients.‡

We believe that combined puncture is a safer method of obtaining lumbar fluid in patients with papilledema than lumbar puncture alone. We hope that by this method we may diminish the number of cases in which ventriculography is necessary, because of the disturbing mortality of that diagnostic procedure, a mortality which amounted to eight per cent of the 392 cases recently collected by Grant.[5]

Historical Review of the Development of the Conception of the "Froin Syndrome"

In order to understand the principles upon which our method is based, it is important to trace the development of the conception

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‡ As this goes to press, December, 1925, combined puncture has been used more than fifty times. These cases will be reported by J. S. Hodgson and F. Fremont-Smith.

of the "Froin syndrome" and the significance of earlier manifestations of the same process as indicating cord compression and blockage of the cerebrospinal fluid pathways.

In 1903 Froin[6] reported 3 cases in which the spinal fluid presented a yellow color, clotted spontaneously and contained an excess of cells.

Sicard and Descomps[7] in 1908 were the first to suggest that compression of the cord and constriction of the meninges with formation of a meningeal pouch below the point of constriction were essential to the production of the syndrome—a hypothesis which was placed on a firm foundation in the following year, 1909, by Mestrezat and Roger[8] and Derrien, Mestrezat and Roger,[9] the latter of these two publications being an elaboration of the former and including a study of 12 cases from the literature, and one new case of the authors. These authors correlated clinical and pathological data with the chemical changes found in the fluid and concluded[9] "qu' il y a stase, que la circulation du liquide céphalo-rachidien est localement suspendue, que le liquide ponctioné n'est plus en relation avec le reste des espaces sousarachnoidiens." They were the first to emphasize the importance of the interruption of the cerebrospinal fluid circulation in causing the syndrome. In all these cases the number of cells in the spinal fluid was increased. Sicard and Descomps[7] had concluded that the syndrome was diagnostic of meningitis.

Meanwhile, a few cases of tumor of the cord or meninges had been reported in which the spinal fluid was xanthochromic and clotted spontaneously. Rindfleisch[10] in 1904 reported the first of these, a case of sarcomatosis of the spinal cord. In this case the lumbar fluid was xanthochromic, clotted spontaneously after several hours (the albumin content was 2.4 per cent) and presented an increase in cells. In the same year Dufour[11] reported a similar case, a diffuse sarcomatous involvement of the meninges of the spinal cord. Sicard[12] in 1908 reported 2 cases of spinal cord compression from tumor with xanthochromic fluid which he observed in 1902. In 1909 Blanchetière and Lejonne[13] reported in considerable detail a case of spinal cord compression due to a tumor (sarcoma) of the dura mater. The fluid upon several examinations was constantly yellow, clotted spontaneously, but contained no increase in cells. Post-mortem examination showed that the tumor was only slightly adherent to the cord and that there was no evidence of meningitis. These authors denied that the Froin syndrome was necessarily associated with meningitis. This important contribution proved that an inflammatory process was not necessary for the formation of a xanthochromic spinal fluid with massive coagulation.

Mestrezat and his collaborators,[8,9] commenting on these tumor cases, separated them from those showing the complete syndrome by the absence of a pleocytosis, but point out that interruption of the cerebrospinal fluid pathways is present in both types.

Several important reviews of the literature have appeared.[14] Mix[14] in 1915 gave an abstract of each of the 33 cases from the literature, and added a careful description of his own case. He concluded that an increased cell count was not essential to the spinal fluid picture, but appeared only when an inflammatory process was causing the cord compression.

Five years earlier (1910) Nonne[15] had shown that in spinal cord compression due to tumor the spinal fluid may be colorless and form no clot, but in such

cases the protein content of the fluid will be greatly increased, with little if any increase in cells. He reported 6 cases, 5 of which were verified at operation or post-mortem examination. From Nonne's clinic in 1912 appeared a paper by Raven,[16] in which he tabulated 47 cases of cord compression, including 15 cases of his own. These cases all showed increased protein in the fluid, some showing a yellow color and spontaneous clotting, but not massive coagulation. He concluded that a protein increase with slight or no increase in the cells indicated a compression of the cord, and that the protein increase was due to stasis of the fluid below the site of compression.

The effort on the part of many of the authors quoted to limit their discussion to a particular syndrome has led to some confusion both in terms and in the understanding of the significance of the spinal fluid changes. Thus Derrien, Mestrezat and Roger[9] included only those cases showing an increase in the number of cells; and Mix,[14] while concluding that the presence of cells indicated only the inflammatory nature of the compression, excluded all of Raven's cases[16] because of the absence of a massive coagulation.

The first important correlation of the two syndromes, xanthochromic fluid with spontaneous coagulation (with or without cell increase) on the one hand, and a protein increase as the only abnormality on the other, appeared in 1916, when Ayer and Viets[17] reported 12 cases of cord compression. In one of these cases they were able to follow the transition from a colorless fluid, with an increase in the protein, to a xanthochromic fluid, coincident with the progression of symptoms, and a return to a colorless fluid after operation; thus indicating that the one syndrome is but an earlier manifestation of the other. That such is indeed the fact was clearly demonstrated by Ayer[18] in 1919 when he produced both syndromes in cats after experimentally compressing the cord by means of epidural paraffin injections. In one animal (Case 11) he was able to watch the complete syndrome, massive coagulation and xanthochromia, which developed within one day after injecting the paraffin, gradually change during two months to a clear fluid with increased protein as the only abnormality, and later to a normal fluid. Seven combined lumbar and occipito-atlantoid punctures were performed on this animal during a period of two months, and at the last puncture free communication between these two loci was demonstrated. Autopsy showed that the paraffin, originally injected in the lower dorsal region, had diffused as far as the filum terminale, thus explaining how the compression had gradually been relieved.

The application of this combined occipito-atlantoid and lumbar puncture to human cases followed quickly upon the publication, by Wegeforth, Ayer and Essick,[19] in 1919, of the method of performing cisternal puncture in man. The following year Ayer[20] described a series of combined lumbar and cisternal punctures in human cases with spinal cord compression. In this and subsequent contributions Ayer[21,22] demonstrated that, normally, free communication exists throughout the spinal subarachnoid space in man, but that spinal cord compression is associated with blockage of this space, "spinal subarachnoid block."

Thus we may find in the fluid obtained below such spinal subarachnoid block, all gradations in fluid changes from the slightest increase in protein content to massive coagulation and

xanthochromia, with or without a pleocytosis, depending upon the degree, nature and duration of the lesion.

Application of Ayer's Technique to the Study of the Ventricular and Lumbar Fluids in Brain Tumor Cases

We have reviewed the fundamental work by Ayer in some detail because it shows the gradual development, on a sound basis, of the technique of combined punctures with the coincident hydrodynamic and chemical study of the fluids from the different loci. This forms the groundwork for our present study. We have simply taken the technique as developed by Ayer and applied it to the study of the relationship between the ventricular and the lumbar spinal fluid, particularly in the presence of brain tumors.

That such application can be made naturally depends on the presence of the same free communication between the ventricles and the lumbar subarachnoid space that exists between the cisterna magna and the lumbar sac. Dandy and Blackfan,[23] Dahlström and Wideröe,[3] Solomon, Thompson and Pfeiffer[4] and Ruggles[33] have clearly demonstrated this point.

The first* direct application of Ayer's technique to intracranial conditions was reported by Ayer himself[20] in 1920. In a case of meningitis he demonstrated a free communication between the lateral ventricle and the cisterna magna by means of combined ventricular and cisternal puncture.

Not only is there free communication between the ventricles and the spinal subarachnoid space, but in the strictly horizontal position the cerebrospinal fluid pressure in these loci are normally equal (just as they are equal in lumbar sac and cisterna magna). This has been demonstrated by Solomon,[32] Ayer and Mixter[24] and by ourselves.

That blockage of this communication may be caused by various agencies (quite analogous to spinal subarachnoid block) is recognized. Thus it is generally accepted that tumors of the posterior fossa cause an internal hydrocephalus by obstructing the circulation of the cerebrospinal fluid either by preventing its outflow from the third or fourth ventricle, or interfering with its free passage forward from the fourth ventricle to the cisterns at the base of the

* Since this was written, an article by Cushing has appeared, showing that many years ago he had performed combined lumbar and ventricular puncture, demonstrated normal free communication and parallel pressure between these regions and that he had noted block between the ventricles and the lumbar region in a case of meningitis. (*Lancet*, Lond., 1925, ccix, 851.)

the brain. A similar condition, caused by adhesions, is found in post-meningitic hydrocephalus. The first evidence of a mechanical block was furnished by Magendie[25] in 1825 who described an anatomical obstruction at the base of the brain. Since then obstruction between the ventricles and the spinal subarachnoid space has been mentioned by numerous writers. Oppenheim,[26] in discussing lumbar puncture states that "Puncture may yield no fluid when the communication between the vertebral canal and the cavity of the skull is obstructed by the closure of the foramen of Magendie, e.g., from adhesions and growth of the meninges; in distension of the ventricles, also, the outflow may be hindered in a purely mechanical way by pressure of the brain against the bones or by pinching of the aqueduct of Sylvius (Quincke) or by the cerebellum and medulla being jammed into the foramen magnum."

How effectively such conditions may obstruct the cerebrospinal fluid is made clear by Cushing[27] (Case IV) in an operative note on a case of a cerebellopontine-angle tumor: "The dura was widely opened and the incision was carried down in the median line to the upper margin of the atlas The cerebellum protruded markedly and its herniated lips, which constituted a marked pressure cone, were then gently drawn up from the spinal canal."

And again (Case VIII), Cushing stated, "Dura very tense: marked foraminal pressure cone: very little fluid obtained; posterior arch of atlas removed: dural incision carried down to arch of axis, exposing cord below lower edge of cerebellar pressure cone; abundance of fluid escaped with immediate resumption of spontaneous breathing one hour after its cessation."

That such obstruction may modify the hydrodynamic as well as the chemical content of the fluid obtained at lumbar puncture is also referred to not infrequently in the literature. Bing,[28] discussing neoplasms of the posterior fossa, said, "If lumbar puncture be resorted to, pressure falls rapidly and the flow of cerebrospinal fluid very soon ceases. Apparently the tumor suddenly presses the medulla into the occipital foramen and so blocks the communication between the intracranial and spinal fluid." Bing justly emphasized the danger of sudden death in such cases due to respiratory failure following lumbar puncture.

In the discussion of the paper by Ayer and Viets,[17] Dr. Francis A. Ely mentioned a case of posterior fossa tumor in which the lumbar fluid was yellow and had a high protein content. Dr. Charles A. Elsberg also spoke of 3 cases of tumor near the cere-

bral ventricle in which both the ventricular and the lumbar fluids were yellow. He did not state whether the punctures were made simultaneously.

Cushing[27] mentioned finding a yellow fluid in the lateral cerebellar cistern in cases of a cerebellopontine-angle tumor. According to Scully,[14] the earliest report of a yellow spinal fluid was that of Busch, 1897, quoted by Leschke,[14] a case of sarcoma of the third and fourth ventricles.

Very recently (1924), Eskuchen,[29] in an article devoted to the diagnosis of spinal subarachnoid block, mentioned a case of cerebellopontine-angle tumor in which combined ventricular and lumbar puncture showed a block and an increased protein content in the lumbar fluid. This article did not come to our notice until after our first communication.[1]

It will be evident from the foregoing that in combined ventricular and lumbar puncture we may expect to find conditions analogous to those found in combined cisternal and lumbar puncture. Thus with a patient in the lateral position, manometers attached to lumbar and ventricular needles, provided the two needles are at the same horizontal level, will register equal pressures. Withdrawal of fluid from either locus will cause a simultaneous and equal fall in each manometer. Jugular compression will give a prompt, simultaneous and equal rise in pressure in both the ventricular and lumbar manometer, and on release of jugular compression both fluid levels will promptly fall to within a few millimeters of the original level. Pulse and respiratory oscillations will be noted in each manometer, and these may normally be of slightly greater amplitude in the ventricular manometer. Any change in pressure within the fluid spaces will be registered immediately and equally in the two manometers. These are the normal relationships and are precisely similar to those obtained by lumbar and cisternal puncture.

Complete spinal subarachnoid block manifests itself by abnormal pressure relationships between the lumbar sac and the cisterna magna. Changing the pressure in one locus will fail to register a corresponding change in the other. The jugular compression test is most important. In complete spinal block, no rise will be obtained in the lumbar manometer on jugular compression, while the normal rise and fall will occur at the cisterna magna. In early cases, Ayer[21,22] demonstrated a partial block. This is shown by a relatively slow and slight rise in the lumbar manometer

on jugular compression and the same slow fall upon jugular release.

A tumor or other lesion causing a block between the ventricular and lumbar spaces should manifest itself in the same way. A complete obstruction to the outflow of cerebrospinal fluid from the ventricular system will result in death in a short time if the cranial sutures are ossified. When the outflow is partially restricted, the rising intraventricular pressure tends to keep the partial communication open. Complete block, therefore, is not to be expected until late. We have had no such case.

Ayer made use of chemical as well as hydrodynamic differences in the two fluids, and emphasized the fact that the increase in the protein content in the fluid below a partial spinal subarachnoid block may occur earlier than demonstrable differences in hydrodynamic relationships. An increase in the protein is also found below certain brain tumors, and may be striking when there is little or no evidence of dynamic block.

Normally the ventricular fluid protein value is less than half that found in the lumbar fluid. Cestan, Riser and Laborde[30] gave 10 mgms. per 100 c.c. as the normal value in the ventricular fluid and 30 mgms. as the normal value in the lumbar fluid. In the absence of a tumor or other lesion which lies within the ventricle or which involves the ependyma, we have found the ventricular protein values to range between 5 and 15 mgms. per 100 c.c., while normal lumbar protein values lie between 12 and 40 mgms. per 100 c.c.

Analysis of the Author's Cases

Of our 21 cases, 10 presented subtentorial lesions which were proved either by autopsy or operation (see Table XXIII). Of these 10, 9 showed a partial block between the lateral ventricle and the lumbar sac, which was demonstrated by combined puncture. The lumbar protein value was increased, in these cases, and varied from 56 to 400 mgms. per 100 c.c., with the exception of 2 cases of tumor of the fourth ventricle, in which both lumbar and ventricular protein values were within normal limits. It is perhaps significant that in the 4 cases in which the lesion was in the cerebellopontine angle, the lumbar protein values were all above 100 mgms., varying from 138 to 400, while the highest lumbar protein value in the other cases was 66 mgms. The one case in which we found no block (Case VII), an acoustic neuroma, showed the highest lumbar pro-

tein of the entire series—400 mgms. per 100 c.c. The ventricular fluid protein value in these subtentorial lesions varied little from the normal, with the exception of one grossly bloody fluid (Case I, right ventricle): the highest value was 27 mgms. per 100 c.c., and the lowest value was 7 mgms. per 100 c.c. Cases XI and XII were doubtful as to diagnosis.

TABLE XXIII

COMBINED VENTRICULAR AND LUMBAR PUNCTURE

SUBTENTORIAL LESIONS

Case No.			Proteins (in mgms. per 100 c.c.) Lumbar	Ventricle
I	Glioma of cerebellum	Block	61	35 right* 18 left
II	Glioma of cerebellum	Block	64	24
III	Extracerebellar arachnoid cyst	Block	66	23*
IV	Extracerebellar arachnoid cyst	Block	56*	27
V	Fourth ventricle tumor	Block	38	7
VI	Fourth ventricle tumor	Block	37	12
VII	Acoustic neuroma	No block	400	13 right 13 left
VIII	Acoustic neuroma	Block	267	8
IX	Cerebellopontine-angle endothelioma	Block	181	15*
X	Cerebellopontine-angle cyst	Block	138	10
XI	Probable fourth ventricle tumor	Block	55	18
XII	Congenital deformity of cerebellum(?); dilated fourth ventricle.	Slight block(?)	47 19	36* 16

*Blood-tinged.

There were 7 cases in which the lesion, tumor or cyst was above the tentorium (see Table XXIV). Combined puncture demonstrated free communication in each of these cases, and free communication was also shown in 2 cases of acute syphilitic meningitis. The protein values in these 2 cases are not included because of the inflammatory nature of the process.

With the exception of Case XIX, the protein content of the lumbar fluid in the supratentorial group varied from normal to a slight increase, 55 mgms. per 100 c.c. being the highest value;

while in the ventricle the values were also either normal or but slightly increased.

TABLE XXIV

COMBINED VENTRICULAR AND LUMBAR PUNCTURE

SUPRATENTORIAL LESIONS

Case No.			Proteins (in mgms. per 100 c.c.)	
			Lumbar	Ventricle
XIII	Parietal arachnoid cyst	No Block	44	16
XIV	Temporofrontal cyst	No Block	55	Bloody
XV	Glioma, frontal lobe	No Block	45	20
XVI	Glioma, frontal lobe	No Block	40	24*
XVII	Glioma, motor cortex	No Block	27	33*
XVIII	Glioma, motor cortex	No Block	26	11
XIX	Glioma, motor cortex, deep	No Block	138	103
XX†	Teratoma, third ventricle		200	129
XXI	Acute syphilitic meningitis	No Block		
XXII	Acute syphilitic meningitis	No Block		

* Blood-tinged.

† In Case XX the lumbar and ventricular fluids were obtained on different days. No definite statement can be made as to the presence or absence of block in this case, although there was no evidence of block at the lumbar puncture.

Case XIX, however, shows a marked protein increase in both ventricular and lumbar fluids. This patient had a large, deep glioma underlying the motor cortex and reaching the surface in two places. There is good reason to believe that this tumor invaded the lateral ventricle. Added significance is given to this case by the findings in Case XX. In this patient, a teratoma lying in the third ventricle, projected into both lateral ventricles. The lumbar fluid showed a protein content of 200 mgms. per 100 c.c., while the fluid from the lateral ventricle, obtained several days later, showed a protein value of 129 mgms. per 100 c.c.

Our cases are too few for more detailed analysis. It would appear, however, that subtentorial tumors are apt to show a block and an increased lumbar protein content, the highest protein appearing in cerebellopontine-angle tumors. Cerebral tumors should not show block; and no marked protein increase is to be expected in the lumbar or ventricular fluid, unless the tumor invades the ventricle; in which case, both lumbar and ventricular fluid protein may be significantly increased. We have had no experience with tumors of the pineal body, the pituitary gland or the pons Varolii.

Method of Performing Combined Ventricular and Lumbar Puncture

In performing combined puncture, the patient is placed in the horizontal lateral position, as for a simple lumbar puncture. The posterior horn or vestibule of the lateral ventricle is entered, usually under local anesthesia. A water manometer (calibrated glass tube 1 to 2 mm. bore) is attached, by means of a three-way stopcock, to the ventricular needle, and the initial pressure is measured. If this pressure is elevated (above 200 mm. of spinal fluid), as is usually the case in brain tumor, the pressure is gradually lowered by removing fluid, drop by drop, until the ventricular pressure is within normal limits. This slow lowering of the ventricular pressure before inserting the lumbar needle is, we believe, of importance in diminishing the danger of medullary compression, for it is the high intraventricular pressure which suddenly forces the medulla into the foramen magnum when the tension below is released. When the ventricular pressure has been lowered to a suitable level, the lumbar needle is inserted and a manometer is attached. The lumbar needle and manometer should have the same bore as those used in the ventricle. Pressure studies are now carried out as described by Ayer[20,21,22] for combined lumbar and cisternal puncture. Particular attention should be observed in the placing of the two needles on the same horizontal plane. If they are not, the difference in height should be allowed for in the manometric readings. In any case in which there is no block, the fluid levels in the two manometers will be maintained in the same horizontal plane.

A block is indicated when the fluid levels in the two manometers fail to respond promptly and equally to changes produced in the cerebrospinal fluid spaces, by jugular compression, coughing, removal of fluid, etc. Of the various tests, the response in the two manometers to jugular compression is the most important and the most reliable for indicating either free communication or a block. In doubtful cases this test should be repeated after fluid has been removed from both loci, as slight degrees of block which were not evident at higher pressures may then be demonstrated.

It should be remembered that the response to jugular compression always occurs in the ventricle, whether or not a block is present. A failure to obtain this reponse in the ventricular manometer indicates that the needle is plugged or that it is not free in

the ventricle: pulse or respiratory oscillations in the fluid level are a good indication that true pressures are being recorded. When a block is present, the respiratory oscillations in the lumbar manometer will be diminished or absent, but the pulse oscillations will still be present.

At the close of the procedure, a small quantity of lumbar fluid is removed for examination. If a block is present, this should be a minimum quantity (3 c.c. are sufficient for cell count, a total protein count[31] and a Wassermann test). Final pressure readings are made and enough fluid slowly removed from the ventricle to bring the intraventricular pressure as low or lower than the final lumbar pressure. We feel that this equalizing of the final ventricular and lumbar fluid pressures is important in reducing the danger of medullary compression in subtentorial lesions.

In our earlier cases air was injected into the ventricles at the close of the procedure. In one such case (Case 11) the patient died suddenly twelve hours later and an autopsy showed a large cerebellar glioma with a marked pressure cone. We feel that air should not be injected at combined puncture, especially if a block is present, but should be deferred until later. With the exception of the above-mentioned case, we have had no deaths which could in any way be attributed to the procedure, nor have we had reactions such as commonly follow air injection.

In most of our cases the diagnosis was made correctly without the aid of combined puncture. In 3 cases combined puncture was of definite help in localization. In no case have the results of this procedure been misleading.

Summary

1. Combined ventricular and lumbar puncture has been performed in twenty-two instances.

2. This method makes it possible to obtain lumbar fluid in all cases, including those with high-grade papilledema, with less danger of medullary injury than with the lumbar puncture alone.

3. In patients with subtentorial tumors some degree of block between the lateral ventricle and the lumbar subarachnoid space may be expected.

4. No such block has been found when the tumor lies above the tentorium.

5. In subtentorial tumors the ventricular fluid protein value is normal, while the lumbar fluid protein value is usually increased,

the highest values obtaining in tumors of the cerebellopontine angle. In cerebral tumors both the ventricular and lumbar fluid is usually normal, except when the tumor invades the wall of the ventricle, in which case the protein may be significantly increased in both ventricular and lumbar fluid.

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Chapter XIII

A MANOMETRIC STUDY OF THE CEREBROSPINAL FLUID IN SUSPECTED SPINAL CORD TUMORS*

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SPINAL cord neoplasms, whether intramedullary, intradural or extradural, sooner or later obstruct the free subarachnoid space and interfere with the circulation of the cerebrospinal fluid. Hence a study of the circulation of this fluid may give data of value in determining the presence or absence of spinal cord neoplasms, by far the commonest lesion producing a block in the cerebrospinal fluid circulation in the subarachnoid space.

It has long been known that compression of the veins of the neck, by interference with the venous outflow from the intracranial contents causes a rise in the intracranial pressure and secondarily in the cerebrospinal fluid pressure. Straining, blowing the nose, coughing or deep breathing, etc., also increase the cerebrospinal fluid pressure.

When a manometer is attached to a needle in the lumbar sac and the veins of the neck are compressed, an instantaneous rise in the fluid within the manometer takes place. Queckenstedt† called attention to the fact that when the subarachnoid space is obstructed, the normal rise which follows compression of the veins of the neck does not take place.

In order to determine the clinical value of manometric studies of the cerebrospinal fluid pressure, the present investigation was begun in 1921, on the clinical material of the New York Neurological Institute.**

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† Zur Diagnose der Ruckenmarkskompression. *Deutsche Ztschr. f. Nervenh.*, Leipz., 1916, lv, 325.

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Since then, the manometric readings have been studied in more than 50 patients with suspected spinal cord tumors and in others in whom a spinal cord tumor was not suspected. Where a spinal cord neoplasm was suspected, the pressure study was made by lumbar puncture alone, for the aim has been to make the lumbar puncture alone yield as much information as possible and to determine the value of such data in the diagnosis of spinal cord neoplasms. It was felt that a thorough manometric study of the cerebrospinal fluid through lumbar puncture alone had not as yet been made, and that this might render possible the determination of the indications for combined lumbar and cisternal puncture as advocated by Ayer.* When the single puncture does not give sufficient data to permit of an accurate determination being made, the very excellent procedure of combined cisternal and lumbar puncture so skilfully used by Ayer and his co-workers is strongly recommended. In this series of cases of suspected spinal cord tumors all except 3 have yielded sufficient data to permit of definite conclusions being drawn from the results of lumbar puncture alone. In only these 3 was it found that combined cisternal and lumbar puncture was indicated.

It is necessary to emphasize the fact that manometric studies of the cerebrospinal fluid do not relieve the neurological surgeon of making a thorough, careful neurological examination. It is only one part of the clinical examination. On the other hand, the neurological examination is not complete in any patient in whom a spinal cord tumor is suspected unless a thorough manometric study of the cerebrospinal fluid pressure has been made.

Methods of Producing an Increase in Intracranial Pressure

The mechanism causing an increase in intracranial pressure by compression of the veins of the neck differs from that brought into play by straining, coughing, blowing the nose or deep breathing, etc. Straining, coughing and blowing the nose cause a rise in intracranial pressure as well as in intrathoracic and intra-abdominal pressure. The intra-abdominal and intrathoracic pressure causes a rise in the intraspinal pressure by interference with the vertebral

* Ayer, J. B. Spinal subarachnoid block as determined by combined cisternal and lumbar puncture, with special reference to the early diagnosis of cord tumor. *Tr. Amer. Neurol. Ass.*, 1921, p. 272.

Spinal subarachnoid block. Its significance as a diagnostic sign. Analysis of 53 cases. *Arch. Neurol. & Psychiat.*, Chicago, 1923, x, 420.

and spinal venous circulation, while compression of the veins of the neck interferes only with the cerebral venous outflow.

In a normal individual in whom a free subarachnoid space exists, straining, coughing, blowing the nose, etc., cause a rise in the the cerebrospinal fluid pressure due to pressure exerted upon the fluid in both the cranial and spinal chambers, while compression of the veins of the neck causes a rise due primarily to an increase in intra-

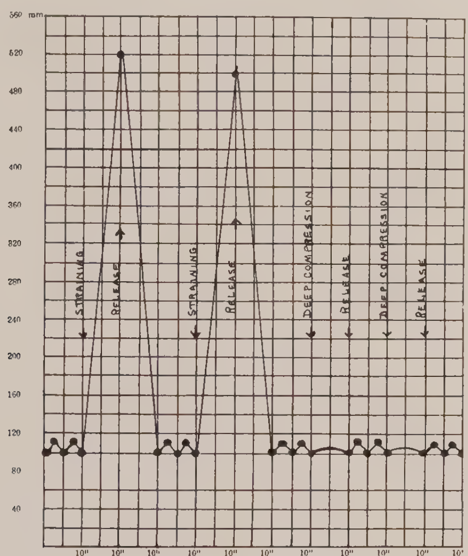

FIG. 5. Manometric chart showing complete subarachnoid block. No rise of the cerebrospinal fluid pressure occurred on deep compression of the veins of the neck, whereas a marked rise occurred on straining. This chart shows that there is a dual mechanism involved in the rise of cerebrospinal fluid pressure: (a) compression of the veins of the neck, causing a rise in intracranial pressure; and (b) straining, causing a rise in intraspinal pressure.

cranial pressure. This point of difference in the spinal and cranial mechanism of pressure increase is of value in interpreting the manometric readings in cases of spinal cord neoplasm. In some instances where complete subarachnoid block existed, a marked rise in the cerebrospinal fluid pressure was found on straining and coughing, but no rise after compression of the veins of the neck. Such a chart is shown in Figure 5, in a patient suffering from a spinal cord tumor which was verified at operation. On compression of the veins of the neck, intracranial pressure was increased and

transmitted to the cerebrospinal fluid *above* the tumor. Due to the block caused by the tumor, this rise in intracranial and spinal fluid pressure *above* the neoplasm caused no rise in pressure in the fluid below the tumor; consequently, no rise in the manometer in communication with the lumbar sac was observed. However, on straining or coughing or deep breathing, etc., without compression of the veins of the neck, a marked rise in the level of the fluid in the manometer took place. Since no rise took place upon compression of the veins of the neck, which of necessity produced an increased pressure above the level of the tumor, and since a rise took place on straining or coughing which increased both intracranial and intraspinal pressure, it may be deduced that the rise obtained was due to a rise in intrathoracic and intra-abdominal pressure transmitted to the cerebrospinal fluid below the level of the tumor. Such a result shows well the dual mechanism involved.

Experimentally it was found that when the veins of the neck were ligated in the cat, a rise in cerebrospinal pressure took place; similarly, when the vena cava inferior was ligated without ligation of the veins of the neck, a rise also took place, showing that either mechanism is effective in producing a change in cerebrospinal fluid pressure. However, the rise in the cat is much slower and not as immediate as in the human being. This difference may be due to mechanical factors present in man and not in the cat. Simultaneous compression of the veins of the neck and the vena cava inferior caused a more rapid rise than compression of either of them alone. By simple compression of the veins of the neck in the cat, without exposing them, the cerebrospinal fluid pressure rose, but to a lesser extent than when abdominal pressure was applied. Abdominal pressure, evenly distributed, was applied to the abdomen by using a blood pressure cuff and a blood pressure apparatus, and caused a greater rise in cerebrospinal fluid pressure than jugular compression.

In earlier clinical work the results of coughing, blowing the nose and deep breathing were investigated, but it was found that these were such variable quantities that comparisons could not be made. Many of the patients, when told to take a deep breath, apparently did not comprehend the command, and, instead of taking a deep breath, merely threw out their chests and held their breath. Likewise, when told to blow their nose, the action and effort expended in the act varied to such an extent that no common factor could be said to exist, and consequently comparisons could

not with fairness be made. However, straining, as if at stool, brought forth in all an effort somewhat more uniform, and while we have had no means of measuring the force exerted, the manometric readings have been sufficiently alike to permit comparisons. To increase the spinal fluid pressure through combined intracranial, intrathoracic and intra-abdominal pressure, we have discarded, consequently, the methods of coughing, blowing the nose and deep breathing, in favor of straining. The procedures used, therefore, were straining and compression of the veins of the neck.

COMPRESSION OF THE VEINS OF THE NECK

Two types of compression of the veins of the neck may be used: first, firm pressure, sufficient to cause cyanosis of the face; and, second, extremely light pressure, which has been called "touch compression." The value of the latter type of pressure has only lately appeared and it has been found to be of even greater value than the heavier form of compression.

In a normal individual light touch compression will produce an immediate fluid wave and cause an appreciable rise in the manometer of from 10 to 30 mm. in the cerebrospinal fluid pressure level, without evoking any straining reaction. The latter, when evoked, causes a rise in intra-abdominal and intrathoracic pressure, and introduces additional complicating factors in the pressure mechanism. Straining or defense reactions may cause a rise of cerebrospinal fluid pressure below the tumor through the action of the factors just mentioned, and unless guarded against, such a rise may be interpreted as the result of compression of the veins of the neck. By touch compression this straining element is not invoked, and the results are those of pure compression of the veins.

The extreme delicacy of touch compression makes it a very sensitive test, and it is believed that it will prove to be of more practical service than the deeper form of pressure, or in any case a valuable adjunct to the other method of investigation.

When firm pressure is applied to the deep veins of the neck and maintained over a period of from five to ten seconds, a great rise in the cerebrospinal fluid pressure takes place. It is conceivable that this may be sufficient, perhaps, to drive the fluid past an incipient complete obstruction, whereas when light pressure is exerted momentarily, the fluid would be less apt to be driven past a blockading mass. Consequently, touch compression may be considered more delicate.

When deep pressure is exerted upon the veins of the neck, the cooperation of the patient must be gained and considerable care used to prevent coughing, holding the breath, or straining. Normally, when firm pressure is applied to the veins of the neck, an instantaneous and continuous rise in the level of the cerebrospinal fluid in the manometer takes place. Within ten seconds or less the fluid level should rise approximately to 500 mm., and as soon as the pressure is removed, an instantaneous and continuous

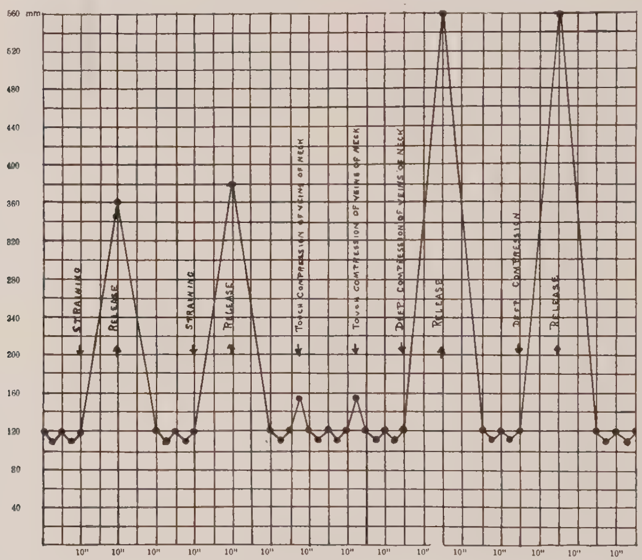

FIG. 6. Typical normal manometric chart showing normal respiratory and pulse oscillations, and prompt rise and fall on touch compression, on straining and on deep compression.

fall should take place, such as is seen when the stopcock of a burette is opened. The fall is generally as prompt, or more prompt, than the rise. Ten seconds or less may be taken as the normal time for the rise and for the fall. The time element is considered to be almost as important as the pressure reading.

A typical normal manometric reading of the spinal fluid is seen in Figure 6.

Technique of Obtaining Manometric Readings

The technique which has now been adopted as the standard is as follows: The patient is placed on his side in a horizontal position and made as comfortable as possible. After the lumbar puncture needle has entered the sub-

arachnoid space, a period of from three to five minutes is allowed to elapse, thus permitting the patient to overcome any pain or fear which may have a tendency to prevent the establishment of the normal level. As soon as complete relaxation is obtained, the reading of the cerebrospinal fluid pressure level is made. This has been termed the stabilized level. Normal pulse and respiratory oscillations of 1 to 3 mm. are usually noted.

Each ensuing step is then explained to the patient in detail, and he is told to do nothing in anticipation of any command until that command is given: not to move or strain, or do anything except remain perfectly quiet until he is told precisely what to do. Unless this is explained, the patient frequently anticipates the command and begins to move toward its execution; whereas the execution should be sudden and its duration timed. The patient's cooperation is more readily obtained when he understands in advance what is expected of him.

Touch compression is then applied over the jugular veins. This type of pressure consists of little more than placing the fingers gently over the veins. When the fingers are placed over these vessels, an immediate and instantaneous rise of 10 to 30 mm. is seen in the fluid level in the manometer. The presence of such an immediate and instantaneous wave generally foretells a negative investigation in the remaining phases of the manometric tests.

The next step is to have the patient strain as if he were at stool, straining for ten seconds. This causes a marked, continuous and steady rise of 200 to 500 mm. A wide variation exists in this test due, in the main, it is believed, to the variation in the force exerted; consequently, the facts gained are considered to be of not too great significance, but at times valuable, as, for example, when a marked rise takes place on straining, with no rise on compression of the veins of the neck (Table xxv, p. 193). At one time it was thought that, in those cases where no rise occurred on compression of the veins of the neck, the result of straining might point to a localization of the block. A small rise might tend to point to a block below approximately the midthoracic region, while a considerable rise would indicate that the level of the block was above this region. The difference in the result of the straining reaction was thought to be due possibly to the fact that in a sac shut off below the midthoracic level, little fluid and a short column would exist below the block and consequently pressure on the short column would cause only a slight rise; whereas when the pressure was exerted upon a longer column with a greater amount of fluid in a more highly placed block, the rise would be greater. While this may perhaps be true theoretically, it was found not to withstand the test of practice in this series of manometric readings.

The next step is to apply firm pressure over the veins of the neck. As a technical procedure it has been found most satisfactory to pass the hands around the side of the neck from behind, holding the palms and fingers flat and avoiding the trachea, so as to interfere as little as possible with respiration. With a little practice, pressure can be exerted without causing the patient to strain or cough. By elimination of straining and coughing, a more nearly pure compression of the veins of the neck is effected, thus avoiding factors introduced when intrathoracic or intra-abdominal pressure is invoked, which, as has been said, may complicate the picture. The pressure is exerted for ten seconds. The rise of the fluid in the manometer should be instantaneous

and continuous to approximately 500 mm. or more, and the recession likewise should be immediate and uninterrupted, when the pressure upon the veins is removed.

As a rule all steps are done twice to lessen the possibility of error, and in some instances, the second compression of the veins of the neck may bring out manometric changes not revealed in the results of the first compression.

Negative Manometric Test in Cases of Intramedullary Tumor

In this series of cases no *extradural* or *extramedullary* or *intradural* tumor was found in any patient in whom a manometric test, negative in all phases, was recorded. To this rule there was no exception. However, in one patient having an *intramedullary* tumor of the conus, a completely negative manometric test was found. In this patient the neurological examination pointed to a very definite intramedullary tumor of the conus. At operation a very slight symmetrical enlargement of the conus, presenting a slightly harder consistency, was found, and a presumptive diagnosis of an intramedullary glioma was made. The rather slight symmetrical enlargement of the cord in this patient did not obstruct the free subarachnoid space. In view of this experience we must therefore consider that intramedullary tumors which give rise to symmetrical enlargement of the cord may, in their early stages, present completely negative manometric readings. Since no type of stasis or obstruction was present with an apparently freely circulating fluid, we feel that examination of the fluid from different loci would not have revealed any noteworthy differences in the fluid, particularly since the lumbar fluid did not show any increase in globulin and only five cells.

Manometric Tests Indicating Complete Block

In all of the patients in whom the manometric findings indicated a complete block, some kind of a definite obstruction in the subarachnoid space was found in those operated upon (Table xxv). In this group of 14 patients showing positive manometric findings, two refused operation, and consequently are unverified. However, their neurological examination left little doubt as to the diagnosis. In the remaining 12 patients operated upon, neoplasms were found in 11, and in the twelfth an extradural tubercular cyst was found blocking the subarachnoid space and compressing the spinal cord in essentially the same way as would an extradural spinal neoplasm.

Thus in all cases of this group verified by operation, an obstruction in the subarachnoid space was determined.

TABLE XXV

MANOMETRIC FINDINGS INDICATING COMPLETE SUBARACHNOID BLOCK*

A. COMPLETE BLOCK; VERIFIED

Name	Level of fluid in manometer, in mm.	Rise on straining; blowing nose or deep breathing, mm.	Rise on compression of veins of neck, in mm.	Fluid		Level	Pathology
				Glob.	Color		
R. Y.	170	320	80	4+	Yellow	C III-V	Glioma, intramedullary
P. S.	140	180	50	4+	Yellow	C VI-VIII	Glioma, intramedullary
A. D.	100	...	0	3+	Clear	C I-II	Endothelioma
C. H.	110	160	40	3+	Yellow	C IV-VI	Neurofibromatosis
L. G.	70	160	0	4+	Yellow	Th I-II	Sarcoma, extradural
M. S.	160	...	0	3+	Clear	Th II-V	Sarcoma, extradural
J. F.	0	100	0	3+	Clear	Th IV-V	Sarcoma, extradural
M. D.	40	80	20	4+	Clear	Th V	Tubercle, extradual
E. P.	100	190	20	4+	Yellow	Th V-IX	Sarcoma, extradural
E. V. H.	100	500	0	2+	Clear	Th VII-IX	Sarcoma
F. Z.	90	180	0	2+	Clear	Th IX	Endothelioma
M. D.	140	200	30	...	......	....	Endothelioma
	Average, 110	Average, 207	Average, 40				

B. COMPLETE BLOCK; UNVERIFIED

Name	Level of fluid in manometer, in mm.	Rise on straining; blowing nose or deep breathing, mm.	Rise on compression of veins of neck, in mm.	Glob.	Color	Level	Pathology
M. A.	100	190	0	2+	Clear	C VIII	
A. P.	80	300	40	1+	Yellow	Th V-VI	
	Average, 90	Average, 245	Average, 40				

* In this group combined cisternal and lumbar puncture is not indicated.

This evidence of obstruction to the free circulation of the cerebrospinal fluid was, however, further substantiated by the fact that in each instance a marked globulin increase was noted. Xanthochromia was present in 5. Xanthochromia without a marked increase in the globulin content was not seen, but a marked globulin increase without xanthochromia was common. In view of the opinion held by some that xanthochromia is not found in intramedullary tumors, it is interesting to note that in both of the intramedullary tumors in this series xanthochromia was present.

In reviewing the neurological examinations of the patients in whom a complete subarachnoid block was found, it is believed

that the diagnosis could have been made from the neurological examination alone by any one with experience in the clinical course of spinal cord neoplasms, irrespective of the manometric findings. The manometric findings merely offered confirmatory evidence in support of the diagnosis. Since lumbar puncture must in any event be performed, it is, of course, reassuring to have further evidence in support of the diagnosis, especially when such evidence can be so readily obtained. We feel that when *positive*

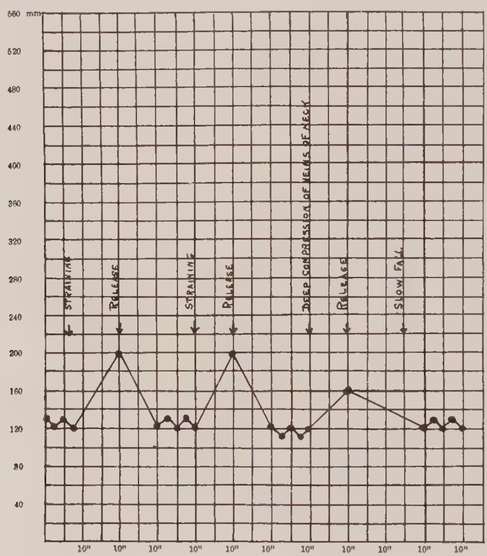

Fig. 7. Manometric chart showing complete subarachnoid block. On deep pressure of the veins of the neck no rise was obtained, yet on straining a slight rise occurred.

manometric findings are obtained through lumbar puncture, no further information of additional value can be gained from combined cisternal and lumbar puncture. A typical positive manometric chart is shown in Figure 7. The positive charts indicating a complete block have been found to follow approximately two types: first, one in which compression of the veins of the neck causes no rise, or essentially no rise, in the level of the cerebrospinal fluid; and second, one in which the rise on compression of the veins of the neck is minimal, seldom more than 50 to 60 mm. It has been difficult to determine whether or not the minimum rise in this

latter group is really due to compression of the veins of the neck or to straining or holding the breath, which in some patients is apparently an unavoidable association. This slight rise is of little significance practically, since such manometric readings can in no wise be confused with the decided rise found when no obstruction exists. Occasionally the slight rise associated with compression of the veins of the neck is sustained a minute or more, the recession being extremely slow and irregular and at times not returning to the old level but establishing a new level, 10 to 20 mm. higher.

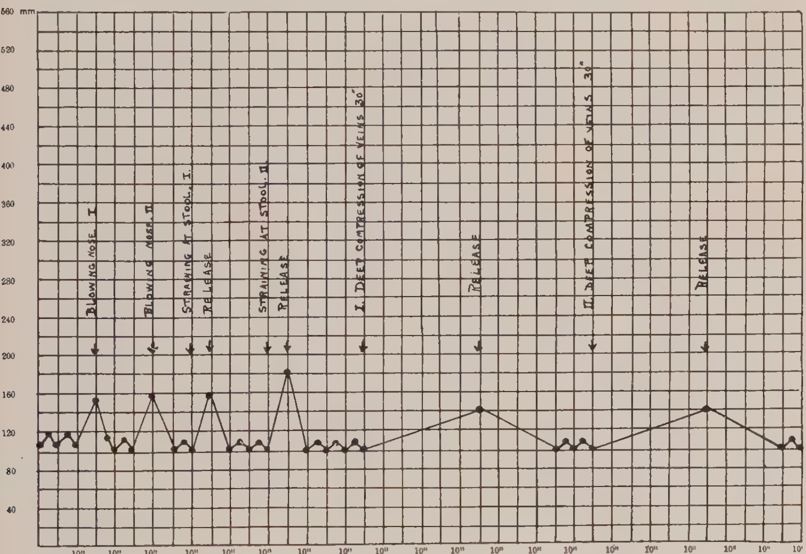

FIG. 8. Manometric chart showing complete subarachnoid block. Very slow and ineffectual rise on compression of the veins of the neck, with a slow return on release of compression.

The pressure readings in the group of complete subarachnoid block are shown in Table xxv. The average initial pressure in the group of complete subarachnoid block was found to be approximately 110 mm. and the average pressure on straining 207 mm., a rise of 97 mm.; while the rise on compression of the veins of the neck was only 40 mm. This is in marked contrast with the manometric readings in normal individuals or in those with an incomplete block. The pressure readings of those showing an incomplete block are seen in Table xxvi. The average initial pressure in this group

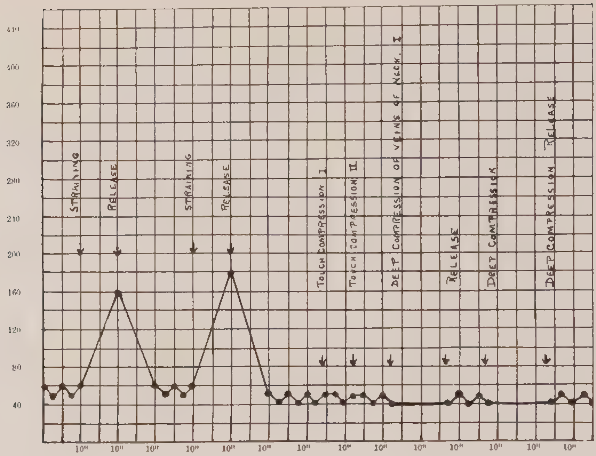

Fig. 9. Manometric chart showing complete subarachnoid block (essentially the same as Fig. 8). The rise on compression of the veins of the neck was minimum, the fall requiring approximately twice as long as the rise.

Table XXVI

Manometric Findings Indicating Incomplete Subarachnoid Block

A. Incomplete block; verified

Name	Level of fluid in manometer, in mm.	Rise on straining, blowing nose or deep breathing, in mm.	Rise on compression of veins of neck, in mm.	Type of rise	Level	Cerebrospinal fluid	
						Glob.	Color
O. S.	100	380	540	Type II			
C. D.	140	510	380	V	..	0	Clear
K. D.	160	260	500	I	..	2+	Clear
F.	160	370	480	I	..	...	Clear
A. H.	100	350	470	IV	..	0	Clear
E. L.	110	460	510	I	..	2+	Clear
J. C.	100	...	220	I	..	0	Clear
	Average, 124	Average, 388	Average, 442				

B. Incomplete block; unverified*

Name	Level of fluid in manometer, in mm.	Rise on straining, blowing nose or deep breathing, in mm.	Rise on compression of veins of neck, in mm.	Type of rise	Level	Glob.	Color
J. S.	100	240	500	I	..	0	Clear
G.	230	...	300	I	..	0	Clear
H. G.	100	340	440	II	..	0	Clear
S. S.	160	510	510	I	..	4+	Yellow
	Average, 147	Average, 363	Average, 437				

* Operation refused or postponed by patient.

In all of this group showing an incomplete block of different types, the full subarachnoid space was definitely compromised in all the verified cases. In the remaining cases sufficient signs were present to make us feel that a definite pathological condition was present.

In other words, incomplete block was not found in any case in which definite signs did not exist.

was found to be approximately 124 mm., with the average pressure on straining 388 mm., or a rise of 264 mm.; while the rise on compression of the veins of the neck was 442 mm. Thus the pressure readings in the latter group approximate those found in normal individuals in whom the subarachnoid space is entirely free. However, the *time* required for the rise, and the *manner* of the rise in those showing an incomplete block are sufficiently different from the normal as not to allow of any confusion.

The pressure in the normal group varies from 100 mm. to 250 mm.; the normal pressure on straining is approximately 300 mm. to 500 mm., and on deep compression of the veins of the neck, the normal pressure may range from 400 mm. to 550 mm. In a normal individual the rise and the fall in pressure are instantaneous, continuous and smooth, without interruptions or the establishment of a new level.

Manometric Tests Indicating Incomplete Block

The manometric findings in this group stand in an intermediate position between the completely positive and the completely negative groups, and represent, pathologically, spinal cord neoplasms or other forms of subarachnoid block in less advanced stages, the subarachnoid space not being completely shut off. Stasis of the cerebrospinal fluid and marked interference with the spinal venous circulation have not yet taken place. From a diagnostic standpoint this group includes those interesting and more difficult cases in which the neurological examination alone is apt to leave the diagnosis in doubt. It is in this group that the manometric tests may be a very great help, since they may aid in determining the presence or absence of an incomplete block; they may also be of value in influencing the conclusion for or against exploratory laminectomy.

In reviewing the neurological examinations alone of the 12 cases included in this group, it was found that in 5 the diagnosis of subarachnoid block seemed warranted without manometric tests; the latter tests in the main serving as confirmatory evidence in support of the tentative diagnosis. From this standpoint such evidence is, of course, reassuring as an additional factor, indicating with greater assurance the advisability of an exploratory laminectomy.

TABLE XXVII

MANOMETRIC FINDINGS INDICATING INCOMPLETE SUBARACHNOID BLOCK DIAGNOSIS CERTAIN WITHOUT MANOMETRIC TESTS; MANOMETRIC TESTS CONFIRMATIVE*

Name		Level	Pathology
S. S.	Unverified	Th X	
O. S.	Verified	C VII	Sarcoma?
E. L.	Verified (*x*-ray)	Th VII	Tubercle of spine
F.	Verified	Th II	Sarcoma, extradural
J. D.	Verified	Th VII-VIII	Meningomyelitis, adherent arachnoid

* In this group combined cisternal and lumbar puncture is not indicated.

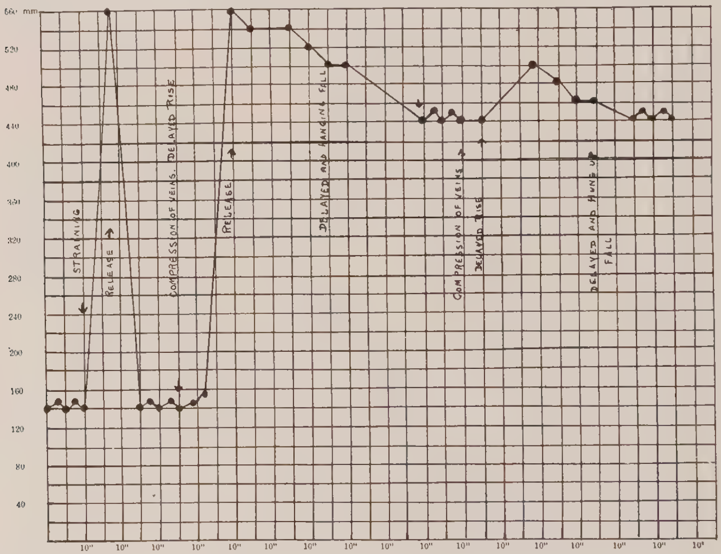

FIG. 10. Manometric chart showing incomplete subarachnoid block—Type I. On deep compression of the veins of the neck, a prompt rise was followed by a hanging fall and the establishment of a new level 300 mm. higher than the original level. Second compression of the veins of the neck showed a slight rise from the new level and again a hanging fall. Note the prompt rise and fall on straining, showing increase in rise of pressure *below* the level of the tumor (see Fig. 5).

In 4 of the group showing an incomplete block, the diagnosis was established by the manometric examination; the neurological examination having failed to give sufficient evidence to warrant the diagnosis of a subarachnoid block. One of these patients showed essentially a cervical root syndrome without any definite signs

of cord involvement. Had it not been for the manometric examination, it is believed that the operation on this patient might have been postponed until more advanced signs had manifested themselves. However, in view of the manometric examination, a more positive stand could be taken, and operation was performed. A very large fusiform enlargement of the cord, presumably an intramedullary tumor, was found. A needle inserted into the cord withdrew a yellow fluid which coagulated almost immediately.

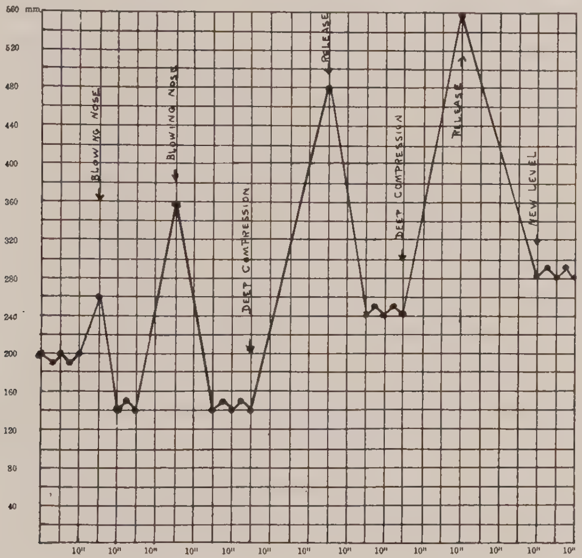

FIG. 11. Manometric chart showing incomplete subarachnoid block—Type 1. Prompt rise on compression of the veins, followed by a prompt fall, with the establishment of a new level 100 mm. higher than the original. On second compression of the veins of the neck a prompt rise and a slower fall took place, followed by the establishment of another level, 40 mm. higher.

TABLE XXVIII

MANOMETRIC FINDINGS INDICATING INCOMPLETE SUBARACHNOID BLOCK

DIAGNOSIS DOUBTFUL. DIAGNOSIS ESTABLISHED BY MANOMETRIC TESTS*

Name		Level	Pathology
C. D.	Verified	C VII	Glioma, intramedullary
K. D.	Verified	Th IV-V	Endothelioma
G.	Unverified	C VII	Malignancy (secondary)
J. O'N.	Verified	Th VI-VIII	Meningomyelitis, adherent arachnoid

* In this group combined cisternal and lumbar puncture is not indicated.

Without the manometric tests it is believed that most of the patients in this group would not have been explored until a later time, when perhaps the chances for complete return of function would have been materially lessened. In this connection may be detailed the history of a patient now in the Neurological Institute in whom a spinal cord tumor, readily removable, was taken out two years after his first presentation before the Fourth and Surgical Division staff conference. While the presence of a spinal cord tumor was considered at that time, sufficient neurological evidence

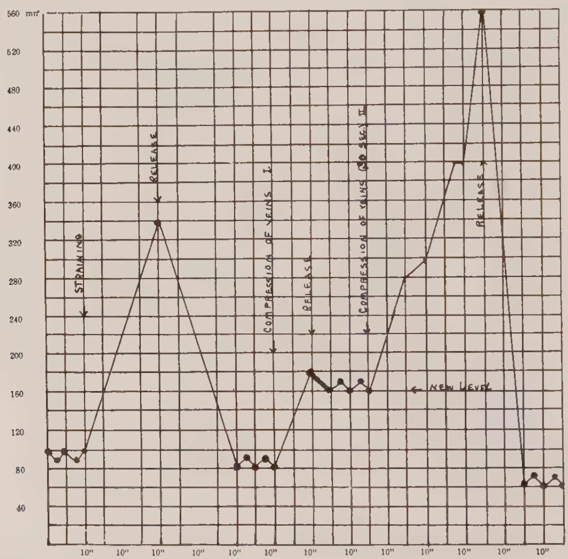

FIG. 12. Manometric chart showing incomplete subarachnoid block—Type 2. On compression of the veins of the neck a rise of approximately 100 mm. took place, with the establishment of a new level 100 mm. higher than the original level. On second compression of the veins of the neck an irregular and labored rise, requiring thirty seconds in place of ten seconds, occurred, followed by a prompt fall approximately to the original level.

was not available to warrant an exploratory laminectomy. No manometric test had been performed, and to this extent the neurological examination was incomplete. Had manometric readings been made, sufficient evidence would perhaps have been gained to warrant an exploration in spite of the inconclusive clinical findings. This patient was lost track of for two years, and on his return marked evidence of the presence of a spinal cord tumor was found;

but so great a destruction of the cord had occurred that in spite of a very skilful operative removal, no return of function has taken place.

TABLE XXIX

MANOMETRIC FINDINGS INDICATING INCOMPLETE SUBARACHNOID BLOCK DIAGNOSIS DOUBTFUL; MANOMETRIC TESTS SUGGESTIVE*

Name		Level	Pathology
A. R.	Unverified		
H. G.	Unverified	Th v	
A. H.	Verified	Conus	Glioma, intramedullary

* In this group combined cisternal and lumbar puncture is indicated.

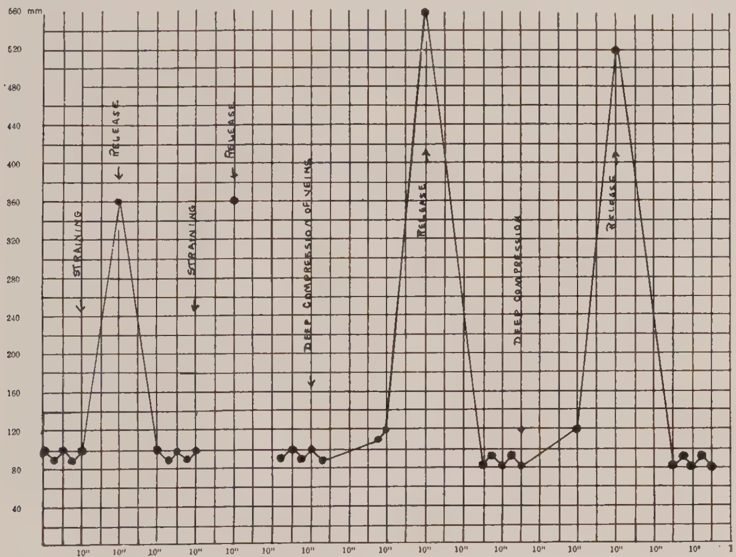

FIG. 13. Manometric chart showing incomplete subarachnoid block—Type 3. On deep compression of the veins of the neck a delay in the rise occurred. The fluid hesitated an appreciable time and then promptly rose and fell.

In an additional group of 3 cases showing an incomplete block, both the neurological and the manometric examination left the diagnosis still in doubt. While the manometric changes were suggestive of an incomplete block, the evidence was so slight that the diagnosis of an incomplete block was considered too doubtful to warrant an exploratory laminectomy. When the manometric

readings are only slightly suggestive and the neurological examination is also indefinite, a combined cisternal and lumbar puncture is definitely indicated. Of the 50 cases of suspected spinal cord neoplasm included in this study, combined puncture was indicated in these 3 only. Combined puncture should be reserved for those cases in which both the neurological examination and manometric readings are indefinite. Combined lumbar and cisternal puncture

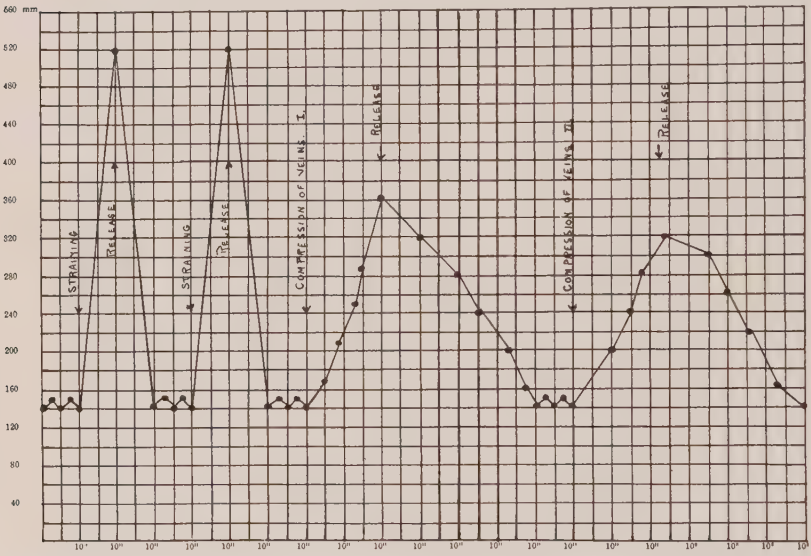

FIG. 14. Manometric chart showing incomplete subarachnoid block—Type 4. On deep compression of the veins of the neck a slow and labored rise and fall occurred. Type 5 is similar to Type 4, the rise and fall being smooth and continuous, but requiring a longer time than normal for both the rise and for the fall.

certainly is not indicated in those cases in which frankly negative manometric tests in all phases are found, or in those cases in which a frankly positive manometric test is found. Combined puncture is not indicated in the other intermediate group in which definite evidence of an incomplete block is gained by the manometric examination; but combined puncture is definitely indicated in the remaining very small group in which neither the neurological nor the manometric examination frankly results in either completely negative findings or those indicating complete or incomplete block. In this *sub-group* of those suspected of having an *incomplete*

block, the greatest help is to be gained by a combined cisternal and lumbar puncture, as advocated by Ayer and his co-workers. Manometric charts indicating incomplete block are shown in Figures 10, 11 and 12.

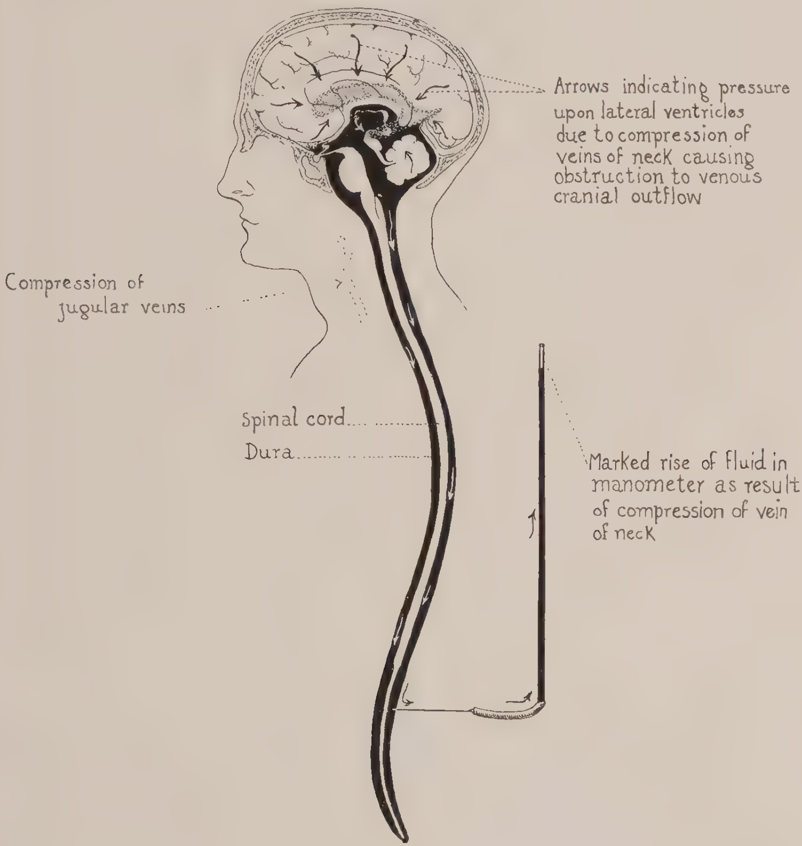

FIG. 15. Schematic drawing showing mechanism of alterations in the cerebrospinal fluid pressure. A marked rise in intracranial pressure takes place when the venous cranial outflow is obstructed by compression of the veins of the neck. The cerebrospinal fluid is forced out of the cranial cavity in the subarachnoid space, causing a marked rise in the manometer in connection with the lumbar sac.

It has been attempted to group the various incomplete charts into five types, but the distinction between each cannot be too sharply drawn. The first three types, and their variations, are indicative of an incomplete block, but Types 4 and 5 are distinctly

less suggestive. In the latter two types the diagnosis of an incomplete block should therefore be confirmed by combined puncture before recommending exploratory laminectomy.

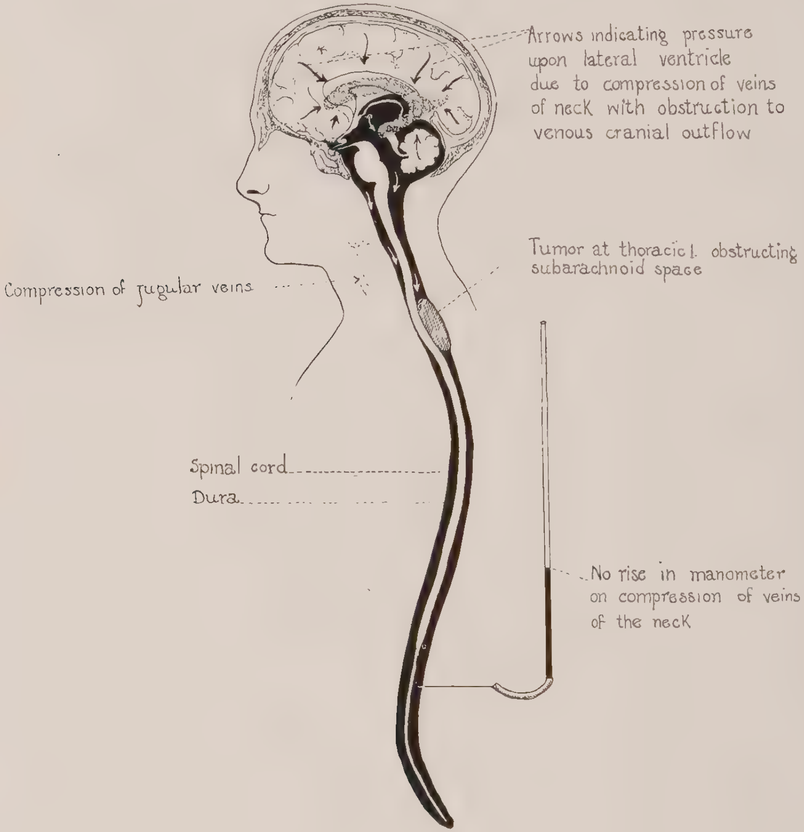

Fig. 16. Schematic drawing showing mechanism of alterations in the cerebrospinal fluid pressure in the presence of a subarachnoid block. Compression of the veins of the neck forces fluid into the spinal subarachnoid space; however, a block in the subarachnoid space does not permit transmission of the increased pressure of the fluid *above* the tumor to the fluid *below* the tumor; consequently, no rise in the manometer in connection with the lumbar sac takes place.

Conclusions

1. In suspected spinal cord neoplasms manometric readings of the cerebrospinal fluid through lumbar puncture should be a routine procedure. The clinical examination is incomplete without a manometric study.

2. Manometric studies of the cerebrospinal fluid through lumbar puncture alone may indicate a complete subarachnoid block,

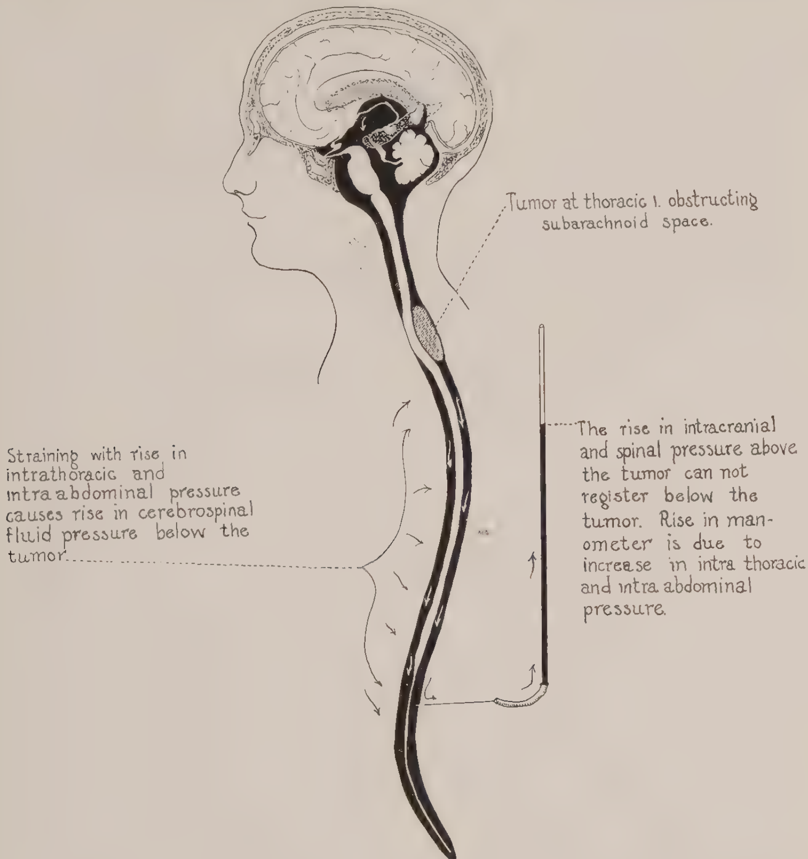

FIG. 17. Schematic drawing showing mechanism of alterations in the cerebrospinal fluid pressure in the presence of a subarachnoid block. Straining causes a marked rise in intracranial, intrathoracic and intra-abdominal pressure; consequently, in a free subarachnoid space all these factors are involved to produce a rise in the cerebrospinal fluid pressure on straining. However, when a subarachnoid block is present, the rise due to increased intracranial pressure is ineffectual, since the fluid *above* the tumor is shut off from the fluid *below* the tumor. The rise in the manometer on straining is therefore due to the intrathoracic and intra-abdominal pressure exerted on the cerebrospinal fluid *below* the tumor.

incomplete subarachnoid block, or the presence of a free, unobstructed subarachnoid space, without resorting to combined lumbar and cisternal puncture.

3. In all patients operated upon, in whom the manometric tests indicated a *complete* subarachnoid block, some form of spinal cord neoplasm was found.

4. In all patients in whom the manometric tests indicated an *incomplete* subarachnoid block, either a spinal cord neoplasm or some other form of subarachnoid block was found.

5. Negative manometric readings were found in one patient having an early symmetrical enlargement of the cord, presumably an intramedullary tumor, which, however, did not interfere with the free circulation of the cerebrospinal fluid. In all others exposed, the manometric findings were substantiated at operation.

6. Combined lumbar and cisternal puncture is indicated when manometric studies through lumbar puncture alone do not permit of definite conclusions being drawn. In this series of cases combined lumbar and cisternal puncture was indicated in only 3 out of 50 suspected spinal cord tumors.

Discussion

The following question submitted to Dr. Stookey before the Commission, together with the answer to it, is here reported verbatim.

Dr. Prince: I should like to ask Dr. Stookey to explain the mechanical or physiological factors involved in muscular tension, straining or other movements which block the circulation in the vertebral and cerebral veins, enclosed as they are within the spine and skull. How do they increase the pressure within the bony canal; within the membranes of the spinal cord? Is it by increasing the volume of the brain on the one hand and the spinal cord on the other, or the meninges, or what?

Dr. Stookey: I do not know that I can give the exact mechanism. The deductions we have drawn from our clinical and experimental work would lead us to believe that the rise in cerebrospinal fluid pressure on straining is due to a rise in intracranial, intrathoracic and intra-abdominal pressure, which temporarily blocks the venous outflow from the cranial cavity and from the vertebral canal, thereby causing secondarily a rise in the intracranial and intravertebral pressure. Experimentally we were able to increase the cerebrospinal fluid pressure by putting a clamp on the vena cava inferior, and on removal of the clamp a fall of the cerebrospinal fluid pressure occurred. The relation between the venous outflow and the cerebrospinal fluid pressure is very delicate. Instantaneous pressure of even one jugular vein will cause a momentary rise of the cerebrospinal fluid pressure, thus showing that the balance is very finely set between the cerebrospinal fluid pressure and the venous outflow.

Chapter XIV

EXPERIMENTAL STUDIES IN THE REDUCTION OF THE NORMAL CEREBROSPINAL FLUID PRESSURE IN CATS BY THE INTRAVENOUS ADMINISTRATION OF HYPERTONIC SOLUTIONS

HUBERT S. HOWE, M.D.

BEFORE presenting the results of the author's experimental studies, the following historical summary of work performed in the reduction of cerebrospinal fluid pressure by hypertonic solutions may be of interest:

In 1919 Weed and McKibben called attention to the fact that it was possible to decrease the pressure of the cerebrospinal fluid experimentally by the intravenous injection of hypertonic solutions. Since the publication of their paper there have been a number of workers who have confirmed their findings and contributed further observations.

Haden was the first to publish his clinical application of this principle. He administered a concentrated glucose solution intravenously to two patients with meningitis and obtained some improvement in their condition, which he attributed to a lowering of the intracranial tension. Cushing and Foley followed this with a demonstration of the possibility of decreasing the brain volume by the intravenous injection of hypertonic solutions. These authors further found that a similar diminution in brain bulk and decrease in intracranial pressure could be obtained by the introduction of hypertonic solutions into the stomach or intestine. Hypotonic solutions, which had been shown by Weed and McKibben to increase the brain mass as well as the cerebrospinal fluid pressure when administered intravenously, were found by Cushing and Foley to have a similar though less pronounced action when introduced into the intestine.

Sachs and Belcher were able to ameliorate the increased intracranial tension occasioned by a brain tumor, through the intravenous injection of 100 c.c. of a 35 per cent sodium chloride solution.

In 1920 Foley and Putnam confirmed the original work of Weed and McKibben, and also demonstrated that the introduction of hypertonic solutions into the gastrointestinal tract would produce similar results. They advised administration by this route not alone because of its convenience, but also because of its safety. The disturbances of circulation and respiration, which were frequently encountered after intravenous injection, were avoided in this way. Thirty per cent sodium chloride solutions were found to be most effective. A saturated solution of sodium sulphate produced similar results,

though less extensive and of slower rate. Concentrated dextrose was less satisfactory, producing still slower and less marked reductions. These authors further believe that the decreased intracranial tension is not due solely to the decrease in brain volume, but primarily represents "new ratios between secretion and absorption of cerebrospinal fluid."

Ebaugh and Stevenson made observations on an epileptic patient who had a defect in his skull occasioned by a subtemporal decompression operation. They confirmed the former observations that hypertonic solutions administered intravenously or orally produced a fall in intracranial pressure. They likewise found a distinct rise in pressure after the ingestion of four to eight liters of water. The intravenous administration of 200 c.c. of a 30 per cent dextrose solution was followed by a fall in pressure which was more gradual and less marked, but more prolonged than that following the injection of a sodium chloride solution.

Sachs and Malone recorded a decrease in the brain volume in dogs following the intravenous administration of a 30 per cent sodium chloride solution. Within ten minutes after administration of the solution a change was noted which reached its maximum in forty-five to sixty minutes. These authors found that the rate of administration of the sodium chloride should not exceed 1 c.c. per minute, since when the solution was given at a more rapid rate there were apt to occur a fall in blood pressure and respiratory disturbance. These workers also used a 30 per cent glucose solution, but without effect.

In 1921 Weed and Hughson published the results of more extended experiments and concluded that, while the normal cerebrospinal fluid pressure is partially dependent upon cerebral venous pressure and to a lesser extent on cerebral arterial pressure, it is for the most part independent of either. They also state that the alterations in cerebrospinal fluid pressure following intravenous administration of hypertonic solutions, while partially parallel to the variations in cerebral arterial and venous pressures, are mainly independent of them and show much more marked depressions.

Dowman, in a clinical application of this principle, advises the use of hypertonic solutions in selected cases of brain injury. He has found it especially valuable in conditions where there has been brain damage with gradually increasing intracranial pressure. He advises the repeated administration of one-half ounce of a saturated solution of magnesium sulphate by mouth or 30 to 50 c.c. of a 30 per cent sodium chloride solution by vein. In a patient who showed evidence of marked increased intracranial pressure, the symptoms were relieved in thirty-six hours by means of repeated injections of salt solution.

Fay found that the intestinal instillation of magnesium sulphate was almost twice as efficient as sodium chloride for the reduction of intracranial pressure. This he attributes to the fact that magnesium sulphate is non-dialyzable, while sodium chloride is readily dialyzed. He also points out that the administration of sodium chloride may produce a secondary wave of edema and increased intracranial pressure due to its absorption and immobilization in the tissues with a subsequent attraction of fluid from the blood stream. Fay calls attention to the fact that over-dehydration is possible and may be serious if not fatal.

Object of Study

On beginning this work, it was felt that the following points had been satisfactorily established:

1. The intravenous administration of some hypertonic solutions will cause a definite fall in cerebrospinal fluid pressure and diminution of brain volume.

2. The fall in cerebrospinal fluid pressure is usually accompanied by a moderate decrease in the systemic venous pressure. The intracranial pressure may be influenced by this venous pressure depression, but is mainly independent of it.

3. The instillation of certain hypertonic solutions in the gastro-intestinal tract will produce results similar to those obtained by intravenous administration.

The object of the following studies was to determine if possible what solutions were least toxic and most efficient in lowering intracranial pressure when given intravenously.

Experimental Methods

Cats were the animals used in these experiments. They were anesthetized with ether by the intratracheal method. This anesthetic has been found suitable by other workers who demonstrated that with it, constant pressure readings were obtained over long periods if an even depth of anesthesia was maintained. These experiments have confirmed this observation.

The cerebrospinal fluid pressures were observed in a glass manometer connected to the lumbar puncture needle by a rubber tube and adaptor tip. The manometer was filled with Ringer's solution and adjusted so that the top of the column of Ringer's solution was at a point 125 mm. above the level of the point of entrance into the subarachnoid space. A lumbar puncture needle was introduced into the cerebello-medullary cistern by piercing the occipito-atlantoid ligament, and connected with the filled manometer system as soon as the obturator in the needle was removed and before more than two or three drops of cerebrospinal fluid had escaped. In this way more accurate pressure determination could be made than when the cerebrospinal fluid must fill the empty manometer. Records of pressures were made at three-minute intervals, and were then recorded as millimeters of Ringer's solution.

No records were made unless there was free pulsation in the manometer. If the anesthetic is administered with a cone, there is ordinarily an excursion of about 4 mm. with each respiration and about 1 mm. for the heart-beat. With the intratracheal method of anesthesia, the respiratory variation is much less marked. An absence of this pulsation usually indicates some block in the manometer system.

The normal pressure values have been given as averaging 112 mm. by Becht, 119 mm. by Weed and McKibben and 133 mm. by Foley and Putnam. The discrepancy may be due to the fact that Becht, and Weed and McKibben apparently used empty manometers, while Foley and Putnam filled the manometer with normal saline solution. The average pressure in this series of experiments was 127 mm.

The administration of hypertonic solutions was made in the femoral vein, either with a syringe or from a burette. The rate of inflow was regulated so that 1 c.c. was introduced per minute. This, after much experimentation, was determined as the satisfactory rate. More rapid injection of some solutions was apt to produce respiratory paralysis.

In order to standardize the dosage, 10 c.c. of a 25 per cent solution were usually employed. When the salt would not form a solution of this percentage, a saturated solution was used.

The observations were carried out over periods of one or two hours.

Experimental Results

Sodium Bicarbonate. Sodium bicarbonate would not be expected to produce marked pressure alterations, as a saturated solution is of such low concentration, being only 9 per cent. Twenty cubic centimeters were used in the experiments.

During the period of injection there is a sharp rise in intracranial pressure of from 40 to 50 mm., which is followed by a sharp drop. The initial pressure is restored about five minutes after the injection is begun and the fall continues for from thirty to forty minutes, when the lowest point is reached. In the experiment shown, the fall was from an original pressure of 125 to a minimum of 78 mm., a reduction of 47 mm. At the end of forty-five minutes, there was a gradual rise which was not observed to its completion. No disturbances of respiration or heart action were observed during or after the administration. Sodium bicarbonate is not toxic to cats, but is not suited for lowering cerebrospinal pressure because of its low solubility.

Sodium Sulphate. This salt was used in a 25 per cent solution. Ten cubic centimeters intravenously produce a prompt rise of from 40 to 50 mm. during the period of injection, which is only slightly greater when 20 c.c. are injected. This is followed by

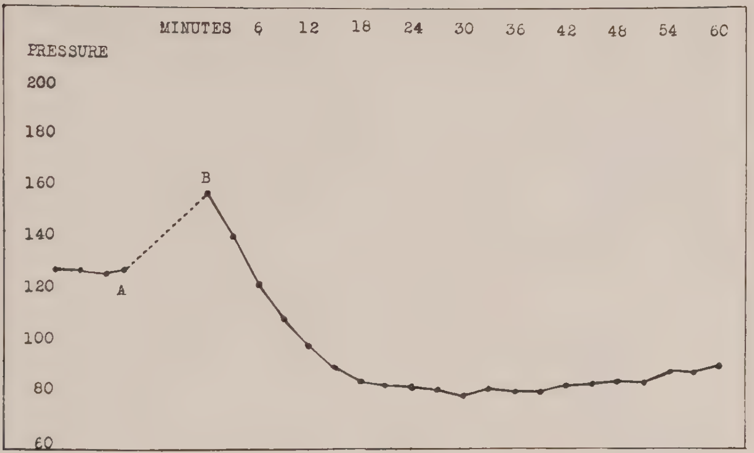

Fig. 18. Cat, weighing 2900 gms. *A* and *B*, 20 c.c. of 9 per cent sodium bicarbonate were given intravenously.

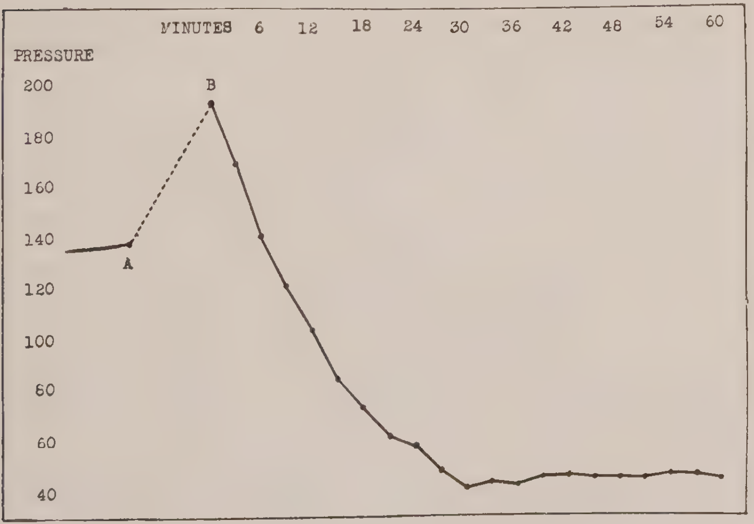

Fig. 19. Cat, weighing 2660 gms. *A* and *B* (10 minutes), 10 c.c. of 25 per cent sodium sulphate were given intravenously.

a rather prompt fall, the pressure reaching the original level in about six minutes and its lowest point in from thirty to forty minutes. The lowest level is usually above zero. No disturbances of respiration, or cardiac action, and no convulsive twitchings

were ever noted. In one experiment 50 c.c. of a 25 per cent solution were given intravenously in less than five minutes, without the slightest disturbance. The pressure rose from 125 to 198 mm. before the pulsations ceased in the manometer and it was evident that the system was blocked. The animal was kept under anesthesia for one hour and forty minutes, and was still in good condition at the expiration of that time.

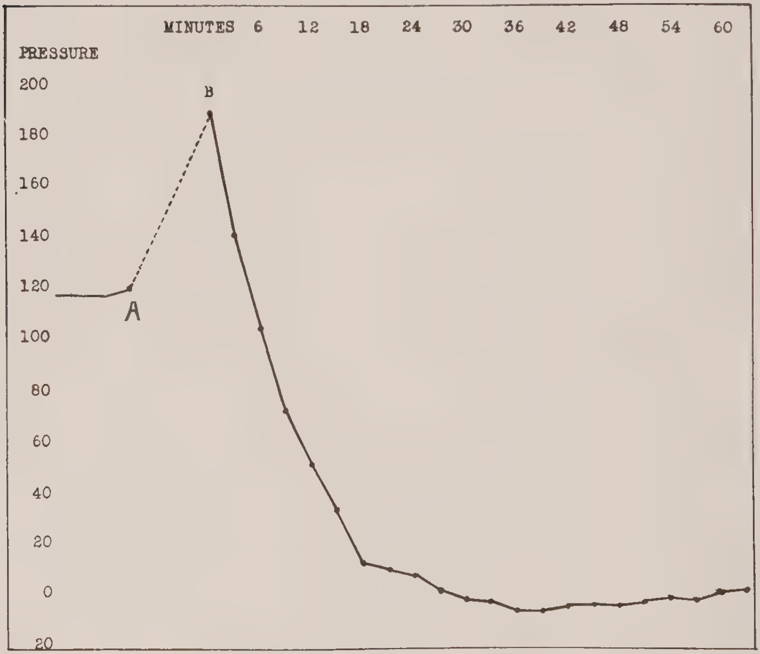

Fig. 20. Cat, weighing 2000 gms. *A* and *B* (10 minutes), 10 c.c. of 25 per cent sodium chloride were given intravenously.

Weed and McKibben noted the absence of any disturbance during the administration of sodium sulphate, but had several animals die later, during their observations, apparently from the toxic effects of this salt. This did not occur in these experiments.

Sodium Chloride. Sodium chloride, of all the solutions used, produces the most striking curves. Ten cubic centimeters of a 25 per cent solution were used in the majority of the experiments. There is a marked rise in pressure during the injection, which may reach 75 to 80 mm. and is usually over 40. This is followed by a very prompt and sharp fall, the pressure usually reaching the

original level within five minutes, and going to zero possibly in twenty to twenty-five minutes. With this salt, negative pressures are at times produced, and the lowest point is generally reached within thirty minutes. Unless the injection is made very slowly, serious respiratory disturbances are observed, as well as cardiac irregularity and convulsions. These may be noted when no more than 1 or 2 c.c. have been injected. Sudden cessation of respiration and death are apt to occur. These toxic effects have been noted by practically all observers who have done experimental work in this field. It is the consensus that this danger may be obviated by very slow administration. No death has occurred in this series of

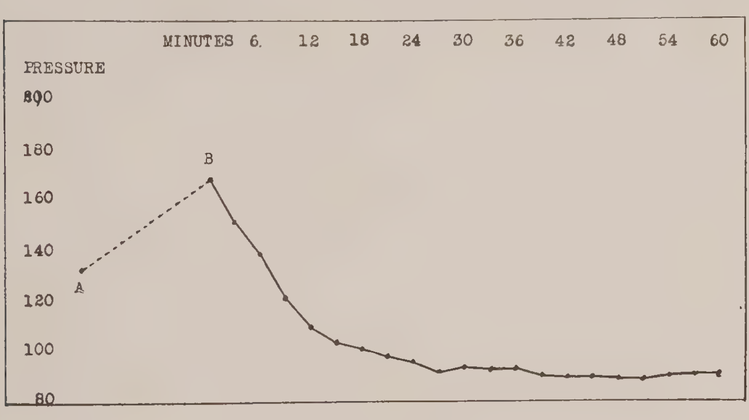

FIG. 21. Cat, weighing 2100 gms. *A* and *B*, 15 c.c. of 18 per cent Ringer's solution were given intravenously (NaCl, 18 per cent; KCl, 0.84 per cent; $CaCl_2$, 0.48 per cent).

experiments in which the administration was not faster than 1 c.c. per minute and in which not more than 10 c.c. of a 25 per cent solution were given. The rate of 1 c.c. per minute, however, is very slow, and is apt to be exceeded unless extreme care is observed.

Weed and Hughson used a concentrated Ringer's solution in which the sodium chloride, potassium chloride and calcium chloride were twenty times the concentration of the normal solution. This gives a sodium chloride concentration of 18 per cent. With this solution these authors found no toxic effects. The result of one of our experiments is shown in Figure 21. The lowering of the pressure, however, was not so great as with a 30 per cent sodium chloride solution, a fact which was borne out by these experiments.

In order to determine a satisfactory reduction in the intracranial pressure, free from the dangers of the pure sodium chloride solu-

tion, some experiments were undertaken with a more concentrated Ringer-Locke solution. The ingredients were multiplied by 27.7, which gives the following formula: NaCl 25 per cent, KCl 1.16 per cent, CaCl 0.69 per cent. The results with this concentrated Ringer-Locke solution were mainly disappointing. It did not seem to be much less toxic than the pure sodium chloride solution of the same concentration, and the reduction of cerebrospinal fluid pressure was not so great. Even 2 or 3 c.c. of this solution, if not injected very slowly, produced interference with respiration. In one cat weighing 2840 gms., 42 c.c. of this solution caused death. In this experiment 10.5 gms. of sodium chloride were administered, which is 3.7 gms. per kilo of body weight. This is the estimated lethal dosage of pure sodium chloride administered in a 10 per cent solution as given by Münzer. This percentage cannot be taken as a standard, however, as it is subject to marked variations.

That sodium chloride is very toxic to protoplasm has long been known, and it was first demonstrated by Ringer that a frog's heart perfused with an isotonic solution of sodium chloride would gradually lose its excitability and cease to beat. He found that if a certain proportion of calcium chloride were added, the excitability returned and spontaneous contractions again occurred. Relaxation, however, was imperfect; but it was found that this could be obviated by adding a small amount of potassium chloride. It was hoped that a well-buffered solution of this kind would be more suitable for this purpose than a pure sodium chloride solution. In order to determine this, a concentrated Tyrode solution was made, having the following formula: NaCl 25 per cent, KCl 0.625 per cent, $CaCl_2$ 0.625 per cent, $MgCl_2$ 0.3125 per cent, NaH_2PO_4 0.156 per cent, $NaHCO_3$ 3.125 per cent, and dextrose 3.125 per cent. Ten cubic centimeters of this solution, injected intravenously, produced a satisfactory lowering of the intracranial pressure. No immediate disturbances were noted when it was injected very rapidly, which was an improvement over the pure sodium chloride or concentrated Ringer's solution. In six experiments, however, all of the animals died before the expiration of two hours.

Sodium Bromide. A 25 per cent solution of sodium bromide injected intravenously was found to be very toxic, 2 to 4 c.c. usually producing paralysis of respiration. In one experiment the toxic dose was calculated as 0.22 gm. per kilo.

Magnesium Sulphate. As would be expected, magnesium sulphate, injected intravenously, is extremely toxic. Two to five cubic centimeters of a 25 per cent solution are lethal to an average-sized cat. In one instance death was produced by 0.18 gm. per kilo of body weight. Death may be preceded by a short convulsion, or may be caused by sudden cessation of respiration.

Calcium Lactate. A saturated solution of calcium lactate produced a sharp rise in cerebrospinal fluid pressure during the injection. In one instance the pressure rose from 154 to 240 mm. as 5 c.c. of this solution were injected, at which time the sudden death of the cat terminated the experiment. The same solution

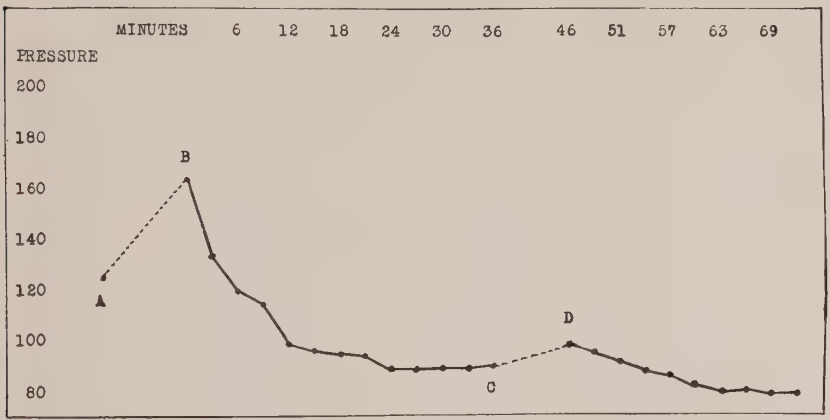

Fig. 22. Cat, weighing 3200 gms. *A* and *B*, 10 c.c. of 25 per cent sodium citrate were given intravenously; *C* and *D*, 10 c.c. of 25 per cent sodium citrate were given intravenously.

was tried with two other cats, but in each instance death occurred before more than 5 c.c. had been administered.

Calcium Chloride. A 25 per cent solution of this salt was unsatisfactory. In three small cats weighing 1800 to 2000 gms., death occurred during administration and before 5 c.c. had been given. In these animals there was no appreciable change in the pressure. In one cat weighing 3060 gms., there was a slight convulsion when 3.5 c.c. had been given, and paralysis of respiration occurred after 9.5 c.c. had been injected, which is .77 gm. of calcium chloride per kilo of body weight. In this instance the spinal fluid pressure rose from 114 to 132 mm.

Sodium Citrate. The intravenous administration of a 25 per cent solution of sodium citrate is accompanied by a rise in

cerebrospinal fluid pressure. In the experiment shown in Figure 22, this amounted to 40 mm. Within six minutes the pressure had regained its original level. It gradually descended to 88 mm.

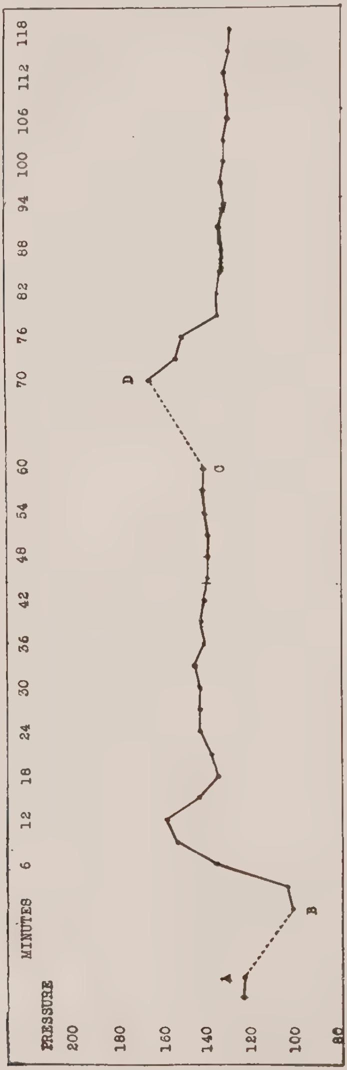

Fig. 23. Cat, weighing 2800 gms. *A* and *B* (10 minutes), 10 c.c. of 25 per cent solution of sodium tartrate were given intravenously; *C* and *D* (10 minutes), 10 c.c. of 25 per cent solution of sodium tartrate were given intravenously.

after twenty-four minutes, and continued at this level for twelve minutes, when a second injection of 10 c.c. was made. This produced very little change. Sodium citrate does not seem to be toxic

in average dosage, though no experiments have been made with rapid injection. It is not very effectual in reducing intracranial pressure.

Sodium Tartrate. Sodium tartrate is the least effectual substance used so far. During the administration, in the instance charted, there was a slight fall in pressure, after which there was a rise of 45 mm. in twelve minutes. Subsequently, there was a fall of 20 mm., with a continuation of about this pressure, which was 18 to 20 mm. above the original reading, for an hour. It is not toxic and even when administered rapidly, it produces no disturbance.

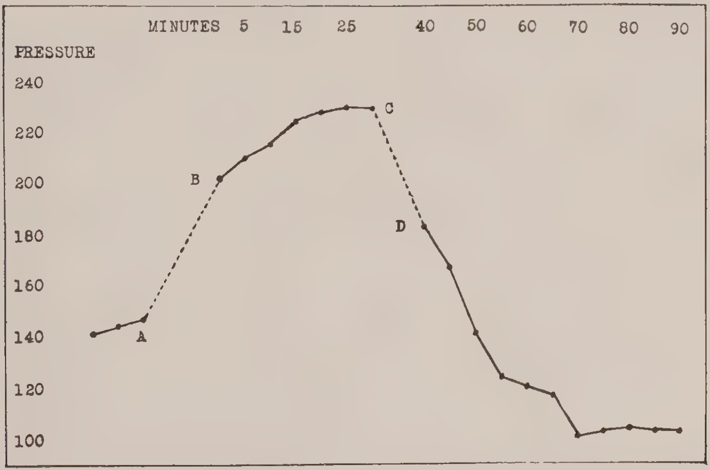

Fig. 24. Cat, weighing 2260 gms. *A* and *B* (15 minutes), 50 c.c. of distilled water were given intravenously; *C* and *D* (10 minutes), 10 c.c. of 100 per cent dextrose solution were given intravenously.

Dextrose. A good many experiments have been made with dextrose. With 10 c.c. of 25 or 30 per cent solutions, no appreciable results have been obtained. With 10 c.c. of a 100 per cent solution, marked reductions in pressure have been observed.

During the injection, there is frequently a rise in pressure which may average 40 to 50 mm. but is frequently much less. The rise terminates with the end of the injection and the fall commences within three minutes. The fall is a little more gradual than with some of the salts, especially sodium chloride, and it requires thirty to forty minutes for the pressure to reach its lowest point. If this is above zero it may be depressed further by additional doses.

The depression is maintained for over two hours, which is as long a period as has been observed.

Dextrose is absolutely non-toxic and has never resulted in the slightest disturbance of respiration or cardiac action, no matter how much was given or how quickly it was administered. Fifty cubic centimeters of a 100 per cent solution have been given in less than one minute without any untoward action.

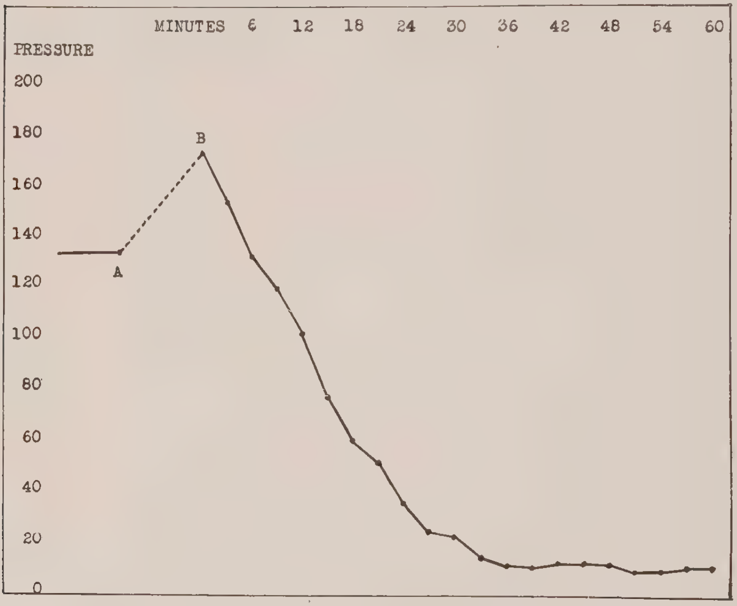

FIG. 25. Cat, weighing 1850 gms. *A* and *B* (10 minutes), 10 c.c. of 100 per cent dextrose solution were given intravenously.

CONCLUSIONS

Experiments have been made to determine the effect of the intravenous administration of various hypertonic solutions on the cerebrospinal fluid pressure of cats. Concentrated solutions of sodium bicarbonate, sodium sulphate, sodium citrate, sodium chloride, sodium bromide, calcium lactate, calcium chloride, magnesium sulphate and dextrose have been used. Also a few observations with a combination of electrolytes have been made in the proportion given in the Ringer-Locke and Tyrode solutions.

Sodium bromide, calcium lactate, calcium chloride and magnesium sulphate were found to be too toxic.

Sodium citrate, sodium tartrate and sodium bicarbonate were relatively ineffectual.

Sodium sulphate, sodium chloride, concentrated Ringer-Locke solution, concentrated Tyrode solutions and dextrose produced satisfactory depressions. Sodium sulphate was non-toxic at first, but has been reported by Weed and McKibben to have caused death later, and so is unsafe for clinical use. Sodium chloride produced the most pronounced decrease in intracranial pressure of any substance used, but is toxic unless administered very slowly. Furthermore, as it is later mobilized in the tissues, producing a secondary wave of edema (as shown by Fay), it is considered unfit for general clinical administration. The same objections apply to concentrated Ringer-Locke and Tyrode solutions, although they are somewhat less toxic.

Dextrose is the only substance of this group which is non-toxic and produces a satisfactory fall in intracranial pressure.

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Chapter XV

THE EFFECTS OF SALT SOLUTIONS OF VARIOUS CONCENTRATIONS UPON CEREBROSPINAL FLUID PRESSURE

W. LLOYD AYCOCK, M.D.

"WHEREFORE, in order to form a just notion of the body of man, it ought to be considered as a hydraulic machine contrived with the most exquisite art, in which there are numberless tubes properly adjusted and disposed for the conveyance of fluids of different kinds. Of these the principal is the blood, from which are derived the several humors subservient to the various uses and purposes of life; and in particular that subtil and remarkably elastic fluid, generated in the brain, and known by the name of animal spirits, the instrument of sense and motion: which functions it never could be capable of executing, were it not contained in proper organs. For this purpose the Almighty Creator has formed two sorts of fibres, the fleshy and the nervous, as receptacles for this active principle; and each sort of these is partly interwoven in the membranes of the body, and partly collected into bundles or cords, and attached to the limbs, for performing their motions with the assistance of the bones."[1]

Thus Richard Mead in 1751 spoke of the central nervous system. In the light of modern knowledge it may still be said that it possesses certain hydrostatic properties.

The are two distinct components of the cerebrospinal fluid to be considered: that portion which is elaborated from the chorioid plexus, and that which is derived from the capillary bed of the central nervous tissue.[2]

Function of the Fluid Elaborated by the Chorioid Plexus

The bony container of the central nervous organs is of relatively fixed capacity and is completely filled with central nervous organs, blood and cerebrospinal fluid. Variation in the volume of any of these elements may occur, compensation being afforded by alteration in the volume of one or both of the remaining elements.[3] This compensatory function is probably the chief one of the

chorioid plexus and the fluid which it elaborates. Other functions of this fluid are, in part, to support and decrease the weight of the fragile and unsuspended brain, to reduce and distribute the force of impacts to which the central nervous organs are subjected and to provide a lubricant between the cranial and spinal walls and their slightly movable contained organs.[4]

Function of the Fluid from the Capillaries of the Central Nervous Tissue

In principle, the fluid circulation within the nervous tissue is analogous to that of other tissues. With reference to the parenchymal cell the system is composed of three elements, the afferent arterial blood supply, the efferent venous outflow and the accessory fluid system which in function is comparable to the lymphatic system of other tissues. There is still considerable uncertainty regarding the mechanism of this system. According to a number of observers, the perivascular system is continuous with a pericellular space, and there is through this channel an uninterrupted exchange of fluid between the parenchymal cell and the perivascular space.[5,6] The outer wall of the perivascular space is an invagination of the pia mater which is brought into the nervous substance by the development of the blood vessels.[7] From an embryogenic point of view, it is perhaps difficult to explain the presence of ganglion cells within a space which is described as a continuation of the mesodermally lined perivascular space.

What seems to be a more tenable conception of this system is that the neuroglia is the medium of exchange between the perivascular space and the nerve cell. This is at first suggested by the sucker or foot-like processes of neuroglia cells which rest on the walls of perivascular channels and by the fact that where nervous elements disintegrate, the proliferating glia envelops and phagocytizes broken-down particles; a portion is resorbed and a portion is carried away in the protoplasmic pathways of the glial reticulum, and thus reaches the perivascular limiting membrane and is pushed through it into the perivascular channel.[8,9,10,11]

Relation of Fluid Circulation to Lesions of the Nervous Parenchyma

In certain diseases of the central nervous system, for example, acute anterior poliomyelitis, there is evidence that the primary lesions are those of the interstitial tissue and that the secondary

nerve cell injury is the result of failure of the blood or accessory circulation, the immediate cause of the cell damage being lack of nutritive fluid, accumulation of catabolic products or the mechanical effects of edema. To combat these effects, methods are to be sought which will increase the passage of nutritive substances to the cell, facilitate removal of its waste products or reduce edema. In addition, specific medication, to be effective, should be carried to the site of the lesion responsible for the cell damage. Recent developments in the use of salt solutions of different

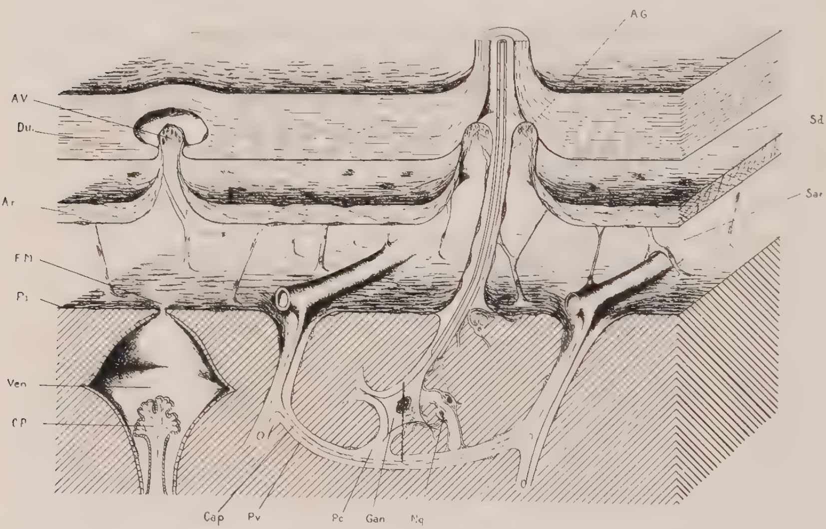

FIG. 26. Schematic representation of the central nervous system, with reference to the circulation of the cerebrospinal fluid. *C. P.* indicates the chorioid plexus; *Ven.*, ventricles; *Pi.*, pia; *F. M.*, foramen of Magendie; *Ar.*, arachnoid; *Du.*, dura; *A. V.*, arachnoid villus; *A. G.*, arachnoid granulation; *Sd.*, subdural space; *Sar.*, subarachnoid space; *Ng.*, neuroglia; *Gan.*, ganglion cell; *Pc.*, pericellular space; *Pv.*, perivascular space; *Cap.*, capillary.

concentrations have opened new avenues of approach to these problems.

The pressure of the cerebrospinal fluid normally bears a certain relation to the pressures of the blood vascular system and undergoes changes corresponding to alterations produced in these pressures. In 1919, Weed and McKibben[12] produced marked alterations in cerebrospinal fluid pressure, which were independent of changes in blood vascular pressures. The intravenous administration of strongly hypertonic solutions lowered cerebrospinal fluid pressure

to an extreme degree. Hypotonic solutions caused a prolonged rise, while isotonic solutions produced only a temporary rise corresponding to the increase in vascular pressures resulting from the intravenous injection.

That the effects of hypotonic and hypertonic solutions on cerebrospinal fluid pressure are due to alterations in the osmotic relations between the blood and the central nervous tissue is shown by changes in the volume of the central nervous tissue and in the perivascular currents.[13]

These findings have been repeatedly confirmed and have led to clinical application of the phenomena. Reduction of hernia and of edema of the brain, and the prevention of leakage of cerebrospinal fluid have been accomplished. The increased passage of substances from the blood to the cerebrospinal spaces is an as yet almost unexplored possibility. The aspiration of suitable remedies from the subarachnoid space into the nervous organs is an important field in the treatment of disease.[14]

Discussion

The following questions submitted to Dr. Aycock before the Commission, together with the answers to them, are here reported verbatim.

Dr. Starr: It may seem trivial in a scientific discussion such as we have had today, to venture upon a mere therapeutic procedure, but I should like to know if such drugs as acetanilid, phenacetin and aspirin, which are notably beneficial in headache, have been examined from the standpoint of their influence upon intracranial pressure? We know that they will relieve intense headaches connected with high blood pressure. I should like to know if there is any real scientific reason for that conclusion.

Dr. Aycock: Certain drugs, as has already been pointed out here today, have been tested for their effects on cerebrospinal fluid pressure, in the reduction of headache. I do not believe that any scientific work has been done on the drugs mentioned by Dr. Starr.

Dr. Strauss: I understood Dr. Aycock's last suggestion to be that the change is due to the capillaries in the interstitial tissue. Now, how do you know that there is no change in either the absorption in these spinal fluid cases or in the filterability of the spinal fluid in the chorioid plexus?

Dr. Aycock: The intravenous injection of hypertonic salt solution changes the volume of the tissue itself. It is not simply the lowering of the spinal fluid pressure.

Dr. Strauss: That has been proved, has it not?

Dr. Aycock: Yes, it has been confirmed by a number of men.

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Section IV

THE DIAGNOSTIC REPLACEMENT OF THE CEREBROSPINAL FLUID BY VARIOUS AGENTS

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CHAPTER XVI

THE CLINICAL VALUE OF VENTRICULOGRAPHY*

FRANCIS C. GRANT, M.D.

THE first reported case of the filling of the ventricular system with air and the subsequent determination of the configuration of the ventricles by contrast between the shadows thrown by the air and the cranial bones was the result of accident and not design. In 1913 Luckett and Stewart[1] x-rayed a skull following a compound fracture of the orbital plate and frontal bone, complicated by a severe sneezing attack with rhinorrhea. To their surprise they found both lateral ventricles clearly outlined on the skiagram. Their explanation was that the increased pressure in the accessory nasal sinuses accompanying the act of sneezing had forced air through the fracture line into the subarachnoid space, which ultimately filled the ventricles. Air, being less dense to x-ray than bone, projected a less dense shadow on the plate and demonstrated the silhouette of the ventricles. This observation passed unnoticed for five years.

In 1918 Dandy[2] suggested the injection of air into the ventricles and subarachnoid system of the brain and spinal cord as a means of defining their outlines on the x-ray plate. While working on the problem of hydrocephalus, it occurred to him that the most practical manner of determining the size of the ventricles and the point of obstruction to the free circulation of the cerebro-

* From the Clinic of Dr. Charles H. Frazier.

Our thanks are due to Drs. Cushing, Horrax, Elsberg, Adson, Sachs, Mixter, Hodgson, Dowman, Rand, Locke and Kanavel for their compilation of the statistics on ventriculography from their clinics. Without their help it would have been impossible to present our summary. Above all, we wish to thank Dr. Charles H. Frazier for his inspiration in preparing this paper and for permission to use his clinical records.

spinal fluid would be to fill the ventricles with a medium which would cast a shadow on the x-ray plate distinguishable from the shadow of the surrounding cranial bones. The ventricles could thus be outlined on the skiagraphic plate, defects in their configuration noted and the point of obstruction to the passage of the fluid discovered. Any substance introduced into the ventricles to outline them by roentgen ray must meet three requirements: (1) It must differ markedly from bone in the density presented to the roentgen ray; (2) it must be non-irritating to the central nervous system, and (3) it must be easily absorbed from the ventricular system. Dandy could find no chemical solution more impervious than bone to roentgen rays that was not too irritating to the central nervous system. He then turned to a medium which after injection would define the ventricles against the cranial bones as a less dense shadow on the roentgen-ray plate. The insufflation of oxygen or atmospheric air proved to be the answer to his problem. The outline of the ventricular cavities filled with air could be clearly seen in contrast to the bone shadow. Air caused no symptoms of irritation to the central nervous system and was absorbed in eight to ten hours from a normal subarachnoid space.[3]

Dandy used intraventricular air injection in the first instance to determine the point of obstruction to the circulation of the cerebrospinal fluid in hydrocephalus. The level at which the block occurred could be readily seen on the roentgen-ray plate, for, as the gas replaced the fluid in the ventricles, it was checked by the same barrier that prevented the fluid from passing freely into the subarachnoid space.

The Anatomy of the Ventricular System

To appreciate the diagnostic value of the injection of a gas into the ventricular system, it is necessary to know something of the anatomy of the ventricles and the physiology of the cerebrospinal fluid contained therein. Within each cerebral hemisphere is situated a cavity containing cerebrospinal fluid, the lateral ventricle. This cavity conforms roughly to the shape of the hemisphere. One arm or horn extends forward into the frontal lobe, another reaches backward into the occipital lobe, while a third passes laterally downward and forward into the temporal lobe. Each lateral ventricle is connected by the foramen interventriculare (Monro) with the third ventricle and through this also indirectly with the lateral ventricle of the other side, but is otherwise completely closed. On the floor of the body of the lateral ventricle and extend-

ing backward and downward from the interventricular foramen into the inferior horn lies the chorioid plexus. This structure is the source of the cerebrospinal fluid. It reaches its greatest development in the lateral ventricle but passes through the foramina of Monro on each side to be continued as the chorioid plexus of the third ventricle. The third ventricle is a narrow, unpaired, slit-like space lying mesially, between and below the frontal horns and bodies of the lateral ventricles. At its caudal end it contracts into a narrow passage, the aqueduct of Sylvius. The aqueduct leads downward and backward in the midline to the fourth ventricle situated mesially beneath the vermis of the cerebellum. The fourth ventricle communicates with the cisterna cerebellomedullaris, formed by the tent-like reflexion of the dura mater and arachnoid across the sharp angle between the lower surface of the cerebellum and the spinal cord, through three minute apertures, the foramen of Magendie in the midline at the lower end of the fourth ventricle and the two lateral foramina of Luschka. The basilar cistern is in free communication with the subarachnoid space of the brain and spinal cord.

The cerebrospinal fluid is formed in the chorioid plexus of the ventricular system. It is absorbed into the blood stream from the subarachnoid space lying over the cerebral cortex. In its pathway from the chorioid plexus to the subarachnoid space the fluid must pass through many narrow straits where obstruction may readily occur. First, on emerging from the foramen of Monro, the only orifice of the lateral ventricle, the liquid reaches the third ventricle and encounters a second constriction in its course, the aqueduct of Sylvius. Through the aqueduct the fourth ventricle is reached, from which the only means of egress is furnished by the fine, slit-like openings of the foramina of Luschka and Magendie into the cisterna cerebellomedullaris. Thence the fluid is carried away by the winding, many-branched channels of the subarachnoid space about the blood vessels at the base of the brain to the area over the cortex, where absorption occurs.

If obstruction, complete or partial, occurs at any point in the ventricular system, a damming back of the fluid above this level results. As the fluid collects and the pressure increases, ventricular dilatation results. By replacing the fluid with air the degree of dilatation and the point of constriction may be shown by skiagraphy. Even the fine threads of air replacing the fluid in the ramifications of the subarachnoid space are distinctly visible. Any change in size, shape or position of the ventricles may be

demonstrated. The insufflated air replaces the fluid and outlines accurately the areas from which it was withdrawn. As the air is followed through the ventricular system, a point beyond which the air should normally pass may be observed. If there is no air beyond this point the site of the obstruction is established.

The normal undilated ventricular system varies but little in size and shape. As a rule it contains from 140 to 160 c.c. of cerebrospinal fluid. The frontal and temporal horns of the lateral ventricles are always found in the same relative position. The occipital horns may be much shortened or may be entirely absent, as has been our experience, as well as that of Penfield.[4] The third and fourth ventricles normally lie in the midline, are very narrow, and often their air shadow is difficult to distinguish. If the ventricular system is patent, air should always be seen in the subarachnoid space. It is only by a proper appreciation of the normal that abnormalities may be determined and correct interpretation of their localizing value be made.

Encephalography

Through his success in the diagnosis of hydrocephalus and the level of obstruction, Dandy had produced convincing evidence that the ventricular fluid might be safely replaced with air by direct ventricular tap. But in dealing with hydrocephalic cases, particularly communicating hydrocephalus, he found that at times it was rather difficult to fill completely the basilar cistern and the cisterna pontis with air introduced from the lateral ventricle. In a second paper[5] he suggests an alternative procedure to solve this problem. The lumbar subarachnoid space is in direct communication with the basilar and pontine cisterns. Following lumbar puncture with the patient in the semi-erect position, the head being above the trunk (at least 20° higher), the fluid is removed, 10 c.c. at a time, by lumbar puncture performed through the fourth lumbar interspace, and an equal or slightly less amount of air introduced. The air rises into the cranium and fills the basilar cistern and ventricles. By this method the subarachnoid space at the base of the brain as well as the ventricles may be clearly outlined and obstruction to the passage of the air revealed. He termed this procedure encephalography to distinguish it from the substitution of air by direct ventricular tap or ventriculography.

From the first he warns that this procedure is more dangerous and may cause a more severe reaction than ventricular puncture.

Particularly is this the case if increased intracranial pressure be present. For a long period it has been realized that lumbar puncture is contraindicated under these conditions. If the spinal fluid which supports the medulla and cerebellum is withdrawn, the supratentorial pressure may force the medulla and cerebellar tonsils down through the bony ring of the foramen magnum. The vital medullary centers are thus compressed against the bone, with disastrous results. While Dandy had no reactions in the 8 cases in which he practised encephalography, he fully realized the possibilities and reserved the procedure for cases of hydrocephalus with no increased intracranial pressure. For other conditions he prefers direct ventricular tap.

Encephalography has been but little used in this country. Martin and Uhler[6] report a series of 14 cases with no fatalities.

The literature of continental Europe furnishes most of the data on this procedure. The cause for the popularity of encephalography among continental surgeons is due to the work of Wideröe[7] and Bingel.[8,9] Curiously enough, these authors first used encephalography to determine the level of a spinal cord tumor. In this they were entirely successful. The air rose to the lower level of the lesion and was held there. A skiagram showed the level of obstruction of the air and the position of the tumor with absolute accuracy. They also noted the interesting clinical fact that removal of fluid and injection of air caused pain in the dorsal roots of the cord segment involved by the lesion. It is believed that the pain is caused possibly by a slight dislocation of the tumor when the fluid which supports and surrounds it is removed or by the passage of the air or fluid about the growth which pulls on the dorsal roots involved by it.

Bingel[10] employed an elaborate technique. Simultaneous lumbar punctures were performed through the third and the fourth lumbar interspaces. Two needles were inserted, one in the fourth lumbar interspace to remove the fluid and insert oxygen and a second needle in the third lumbar interspace attached to a water manometer to record the pressure. Whenever possible, at least 40 to 60 c.c. of fluid were withdrawn and an equal amount of gas injected. Oxygen, bubbled through a solution of bichloride of mercury to insure sterility, was used. He feels that oxygen is absorbed more rapidly than air.

Within a short time after the publishing of these reports, several series of cases were reported. Bingel[11] reports 250 cases of encepha-

lography without a death which might be attributed to this procedure. Alwens and Hirsch,[12] Cestan and Riser,[13] Weigeldt,[3] Denk,[14] and Wrede[14] each report large series of encephalographies without a fatality. Gabriel[15] has performed many cases without serious ill effects.

In analyzing these series of cases, one is struck with the attitude assumed towards encephalography. Much emphasis is laid upon the physiological fact that air may be injected into the lumbar sac with impunity and will pass into the ventricles and the subarachnoid spaces, thus proving that the foramina of Luschka and Magendie are patent. Many of the cases in which the air was injected were normal subjects upon whom the procedure was carried out to note the result. The therapeutic effect was carefully watched. Other authors, Alwens and Hirsch[12] and Bingel,[9] report the successful relief of severe headaches which followed encephalography and which they believed to be due to circumscribed serous meningitis. Dahlström and Wideröe[16] refer to the successful serum treatment of cerebrospinal syphilis following lumbar air injection. The determination of the point of obstruction in hydrocephalus was repeatedly described,[17,18] but it seems very significant that in all the continental literature there is not one case of brain tumor reported which was localized by air injection and removed at operation. Jungling[19] and Denk[20] report tumors localized as deep-seated, inoperable cerebral neoplasms in which a large decompression without attempt at removal of the neoplasm benefited the patient. Halle[21] reports two tumors localized by air injection as too deep-seated for surgical removal and verified later by necropsy.

As we have stated, Dandy,[5] in his original paper, warned against the dangers of lumbar insufflation in cases showing increased intracranial tension. It is curious to note how the more recent German literature echoes his words. After the optimistic reports, already referred to, of large series of cases without fatality, the tone changes. Schott and Eitel[22] state that following encephalography they noted severe reactions, nausea, vomiting, sweating, pallor and shock. Often the subjects were so sick that they could not be moved. Febrile reactions and an intense desire to defecate were observed. While they report no fatalities, they feel that the reactions are too severe to justify the procedure. Mader[17] and Knoepfelmacher,[18] who used the procedure to diagnose hydrocephalus and the point of obstruction in children, record complete collapse,

requiring the use of artificial respiration, as a very frequent occurrence. However, they advise encephalography as the best means of making an early diagnosis of hydrocephalus in children. They do not, however, outline an effective method of treating the condition once the diagnosis is confirmed.

Jungling,[19] Schuller,[23] Denk[24] and Weigeldt,[25] who used both methods, believe that in cases with increased intracranial pressure direct ventricular tap is much safer and of less hardship to the patient than encephalography.

Bingel,[26] who was a strong supporter of encephalography, has collected the fatalities due to it. He has been able to gather records of fifteen deaths following encephalography. In all but two in which data concerning the lesion were given, a brain tumor was present.

Encephalography is not the procedure of choice. It is absolutely contraindicated if increased intracranial tension exists. In determining the level of spinal cord lesions and the point of obstruction in communicating hydrocephalus, it may have a restricted use. Therapeutically, in chronic infectious conditions of the envelopes of the brain and the subarachnoid space, it may be of some value; but the immediate disagreeable reaction that may follow and the fact that it provides us with no information which may not be obtained by ventriculography limit its usefulness.

Ventriculography

Ventriculography has been most widely used in this country. Dandy, after his original work showed that air was well borne by the ventricular system and that the ventricular outline could be seen on the *x*-ray plate, at once realized the possibilities of this procedure in the diagnosis of other intracranial conditions besides hydrocephalus. His next papers[27,28,29] deal entirely with the localization of intracranial neoplasms by ventriculography.

To introduce the air, Dandy enters the occipital horn or vestibule of the lateral ventricle through a trephine opening in the occipital bone, except in hydrocephalic children, where the lateral prolongation of the anterior fontanelle is used. The trephine opening is so placed as to avoid the longitudinal and lateral sinuses. The occipital region is chosen because the largest part of the lateral ventricle is most accessible from this point. The vestibule, on the whole, is less easily collapsed and dislocated than other parts of the ventricle and the vestibules and occipital horns are farther

apart and less easily occluded by the same lesion.[30] A small trephine opening is made in the occipital region on each side. If there is any clue to the position of the tumor, the ventricle on the opposite side is tapped first. The trephine openings are made and the ventricle entered with the patient on his face in the cerebellar position. When the cannula is in the ventricle, the patient's head is turned so that the ventricle entered is in the dependent position. A 20 c.c. syringe with a two-way stopcock is attached to the cannula. The fluid is aspirated into the needle, discharged through the side arm of the stopcock and an equal amount of air is sucked into the syringe and insufflated into the ventricular cavity. The head is rotated gently from side to side to cause the fluid to pass from one lateral ventricle into the other. When all the fluid that can be obtained has been removed and an equal or slightly less amount of air injected, the needle is withdrawn. *X*-ray plates are then taken in four directions, anteroposterior (forehead down), postero-anterior (occiput down), lateral right to left (right ear down), and left to right (left ear down). Briefly, this is the technique almost universally employed in this country. Some surgeons[31] have suggested the injection of smaller amounts of air and, by rotation of the head under the *x*-ray, the outlining of the frontal and occipital horns of each lateral ventricle and the third and fourth ventricles separately. They feel that the insufflation of only a small amount of air is safer and claim equally accurate results in localization. Frequently it may be necessary to tap both ventricles, particularly if the first tap is unsuccessful or is productive of such a small amount of fluid that its replacement by air seems contraindicated.

Denk[20] and Jungling[19] commend tapping the frontal horn of the lateral ventricle. This horn is smaller and harder to enter than the vestibule. Weigeldt[25] advises tapping the temporal horn. This has the disadvantage of the possibility of passing the cannula through the speech centers on the left side. Schuller[23] suggests the use of verticomental and mentovertical *x*-ray exposures, in addition to the more usual views. It is doubtful if sufficient information could be obtained in this way to justify it.

INDICATIONS FOR VENTRICULOGRAPHY

The principal indication for the procedure of ventriculography is the evidence of increased intracranial pressure, the cause of which cannot be localized. Dandy[29] makes the statement that any intracranial lesion of sufficient size to cause an increase in intra-

cranial tension will produce a change in the size, shape or position of some part of the ventricular system. Hence, every brain lesion producing such an increase in tension and furnishing us with no reliable neurological signs upon which to base its position may be localized by determining, through ventriculography, its effect upon the ventricular system and hence its exact location.

STATISTICS ON VENTRICULOGRAPHY

Dandy has never published detailed findings of his experiences. He reports in extenso 3 cases in which the position of an otherwise unlocalizable tumor was accurately determined by ventriculography and the growth successfully extirpated.[27,28] In a brief review of a series of 101 brain tumors,[32] he found that in 35 instances the neurological signs were so indefinite that ventriculography was used. The situation of otherwise unlocalizable lesions was determined and verified at operation on 33 ocasions. Twice he misinterpreted the ventricular shadows on the *x*-ray plate and failed to find the lesion.

Following in Dandy's footsteps, other neurological surgeons have used ventriculography. Davenport[33] reports 28 cases, 11 of which were operated upon. The air localization was confirmed in these operated cases in every instance. Merrill,[34] Towne[35] and Rand[36] describe single cases of neurologically unlocalizable tumor, the position of which could be determined in this way. Towne found a gliomatous cyst which was tapped with much benefit, while Rand was able to extirpate the lesion. The tumor Merrill reports was calcified and its position known, but the air reaffirmed its location.

Through the courtesy of the members of the Neuro-Surgical Society, who were generous enough to furnish their results, it has been possible to compile a series of 392 cases of ventriculography. In weighing the clinical value of this procedure, it was sought to answer the following questions: (1) In how many instances has the ventriculogram been of localizing value in the *presence* of definite neurological evidence as to the situation of the lesion, and in the *absence* of such signs? How often was the presence of a lesion excluded by air injection? (2) What percentage of tumors localized by air injection could subsequently be removed at operation? (3) In how many instances were the *x*-ray films incorrectly interpreted and the tumor not found in the suspected area? (4) What was the number of cases in which, due to errors in technique,

the ventricle could not be tapped; or, if tapped, insufficient fluid could be withdrawn to justify the insufflation of air; or in which, even after air was injected, the *x*-ray picture could not be interpreted? (5) What was the number of deaths resulting directly from ventriculography?

The statistics of McConnell[37] and Jefferson[38] are sufficiently complete to be included in this summary.

Total Cases: 392

I. Cases in Which Ventriculogram Has Been of Localizing Value			311 (79.3 per cent)
A. Confirmatory of neurological diagnosis		124	
Percentage of all cases	31.6		
Percentage of localized cases	40.0		
B. Absence of neurological signs		93	
Percentage of all cases	23.7		
Percentage of localized cases	30.0		
C. Localization probably correct, but unverified		79	
Percentage of all cases	20.1		
Percentage of localized cases	25.4		
D. Tumor suspects ruled out by ventriculogram		15	
Percentage of all cases	0.3		
Percentage of localized cases	0.4		
II. Tumors Localized by Ventriculogram Alone and Susceptible of Operative Removal			44
Percentage of all cases	11.2		
Percentage of localized cases	14.1		
III. Operative Errors Due to Ventriculogram (verified at necropsy or by subsequent history of case)			12
Percentage of all cases	0.3		
IV. Errors in Technique			40
Percentage of all cases	10.1		
V. Mortality Following Ventriculogram			32
Percentage of all cases	8.1		

In addition, the following deaths due to ventriculography have been found in the literature (the reports of Grant[39] and Adson[40] are included in the above summary, hence the fatalities they report are not included in this series):

Dandy[41]: 3 deaths, lesion not described

Bassoe and Davis[42]: 1 death, inoperable cerebral glioma

Towne[35]: 2 deaths, hydrocephalic infants

Merrill[34]: 1 death, hydrocephalus

Wrede[14]: 2 deaths, fibroma of aqueduct, echinococcus cyst of cerebrum

Elsberg[43]: 2 cases, lesions not described.

Of the 32 cases in the summary on page 236, 19 occurred in gliomatous tumors, of which 4 were hemispheric and cystic. These might have been benefited by surgery if the cyst could have been tapped. Seven were solid, deep-seated gliomata and inoperable. Two were cerebellar gliomata, one cystic and one solid. One death occurred in a hydrocephalic child, always a hopeless outlook. The other two deaths followed ventriculography in the presence of a deep tuberculoma of the temporoparietal lobe and of a centrally situated endothelioma of the same region. The latter was one of our cases. The patient was in desperate condition, but if we had performed the air injection more skilfully, he might have survived. It is striking the number of times death occurred in the presence of a gliomatous tumor.

MORTALITY IN VENTRICULOGRAPHY

The cause of death in these cases seems to be due to the following factors: Sudden release of high intracranial tension in the presence of a glioma seems to have the tendency to cause the rupture of small blood vessels in and about the tumor, with subsequent hemorrhage into it. Release of tension may cause spontaneous rupture of the blood vessels in the walls of the ventricles, with hemorrhage. The exploring cannula may pass through the tumor and produce bleeding or penetrate the tumor, where it projects into a ventricle and, by tearing a vein, produce intraventricular bleeding. The intracranial tension may be nicely balanced, and in the presence of a glioma mere release of tension may set on foot a train of unknown physiological changes within the brain, resulting in marked increase of pressure, medullary edema and a fatality. Air per se does not apparently affect the central nervous system. An increase in the cellular content after air insufflation has been claimed by some authors (Herrman[44] and Knoepfelmacher[18]) but denied by others.[25] Air only remains in a patent ventricular system for from eight to ten hours.[3] The condition of patients harboring gliomatous tumors may change suddenly for the worse on merely tapping the ventricle without removing more than a few cubic centimeters of fluid and without the injection of any air. Putting aside the cases in which the exploring cannula actually ruptures a vessel and causes bleeding, it is believed that the serious symptoms due to ventriculography are caused by sudden changes in intraventricular pressure. This factor may be eliminated in great

measure by careful manometric pressure readings, slow withdrawal of fluid and the insufflation of air as the fluid is removed to keep the tension as close as possible to its original level.

The mortality rate in ventriculography should be stressed because it is felt that it is a dangerous procedure. Dandy[30] has admitted this and warned us of it. He has suggested "ventricular estimation as a substitute for ventriculography in those cases whose condition seems serious enough to contraindicate air injection." Both occipital horns are tapped and by measuring the fluid obtained from each, noting the depth at which the vestibule is reached and whether or not a dye injected into one ventricle is recovered from the other, a fairly definite conception of the position of the lesion may be obtained. No air is injected. His report includes a description of tumors localized and removed in this way.

But is ventriculography too dangerous? When one considers that the mortality rate of unlocalizable tumors is 100 per cent, to refuse to perform ventriculography upon a patient who certainly harbors a brain tumor which cannot be localized, simply because it is feared that he may die and thus increase the mortality rate, is as heartless as refusing to jump overboard to save a drowning man because of the danger of wetting our clothes. The 39 patients in the collected series from whom tumors were removed, localizable only by ventriculogram, would all be dead if there had not been the willingness to take a chance. The mortality rate is high, but every case with a tumor (and over 90 per cent of these cases showed neoplasms) reported as a mortality in that series was doomed unless the tumor was removed. Ventriculography only robbed most of them of a very short span of unhappy existence. The errors in technique are many; but as experience is gained, the mistakes will be reduced. In a certain number of patients errors will be unavoidable. The ventricles will be so compressed that attempts to enter them will fail, or they may contain so little fluid that no air can safely be injected. Injection of the air is the easiest part of the technique. It is through correct interpretation of the *x*-ray that the exact localization is made. Neuro-surgeon and roentgenologist should work in unison to perfect a technique which gives the highest possible percentage of correct determinations of the situation of the tumor with the least number of severe reactions on the part of the patient. If the lesion be localized exactly, the degree of its operability may be determined and the craniotomy can be performed directly over the tumor. If on

exposure the neoplasm is infiltrating and inoperable, it is unfortunate, but the sufferer has been given every chance.

The difficulties in diagnosis and chance of error should not be overlooked. Large hemispheric growths are usually easy to localize. It is the tumors lying in or below the third ventricle that present the most puzzling problems. A bilateral symmetrical dilatation of the lateral ventricles exists. Is the obstruction above or below the tentorium? The answer to this question is important, for the surgical approach to subtentorial tumors is a much more formidable affair than a supratentorial exposure. The decision depends upon whether or not the third ventricle and aqueduct are dilated. Often it may be difficult to see moderate degrees of dilatation of these structures, for but little air may reach them. Posterior fossa lesions, by obstructing the lower part of the fourth ventricle, usually cause expansion of all the fluid spaces above this level and are more readily localized, for the air usually reaches a widely dilated third ventricle and aqueduct. At times, with the help of air injection, the situation of the neoplasm may be determined by exclusion of suspected areas, and in this way a correct diagnosis may be made.

The fact that, in the collected series of cases containing the first reports from these clinics (in spite of all the errors due to inexperience and lack of proper appreciation of the problem and its difficulties), the ventriculogram was of definite localizing value in 79.3 per cent of the cases speaks for itself. With further experience the percentage of successes should unquestionably increase.

Conclusions

Our opinion concerning ventriculography is this. It is dangerous. It should not be used indiscriminately. Every other means of arriving at a correct localization of the lesion should be exhausted first. If we are convinced that the patient has a brain tumor, it then becomes a question of expediency. He will die unless it is removed. Palliative decompressions are useless; they accomplish nothing and are a confession of defeat. Exact localization followed, if possible, by radical removal is our aim. Ventriculography, under such circumstances, will provide more positive information about the situation of the lesion than any other procedure. It is our firm conviction that no patient should be given a hopeless prognosis and sent away to die as comfortably as may be, because we are unwilling to risk an immediate mortality through the use of ventriculography. The

tumor once localized and exposed may prove inoperable. That is unfortunate, but is no reason for refusing to try to find out positively whether or not such is the case. The ventriculogram may prove inconclusive, which again is a misfortune; but until we have attempted air injection we have no right to tell the patient that he has an unlocalizable intracranial neoplasm and is beyond our help.

Discussion

The following questions submitted to Dr. Grant before the Commission, together with the answers to them, are here reported verbatim.

Dr. Favill: By just what criteria was it decided that death was directly due to ventriculography: what was the time interval, etc.?

Dr. Grant: I cannot answer that, so far as the statistics of the other investigators are concerned; but in regard to our own fatalities, we have viewed the situation as follows: If a patient dies following ventriculography, we are compelled to put it down as a death due to the procedure, though we may not believe that it caused the death. That is a hospital rule. It is unfair to the procedure, but it is unavoidable. I should say there has been no question, however, in our mind that at least 5 of the 6 deaths that have occurred were directly due to the ventriculography. They all occurred within seventy-two hours of the time that the ventriculography was performed. One man on my service at the Post Graduate Hospital, who had an arachnitis, lived for ten days and was up and around the ward. He went to stool one day, strained and died. I considered his death due to the ventriculography because when we *x*-rayed him, we found that air was still present in the ventricles. There was no hemorrhage; nothing that you could blame on the ventriculography. The hospital rule to which we adhere is that if anyone who is in the hospital and has had a ventriculography dies, his death is considered as due to the ventriculography.

Dr. Kennedy: Dr. Grant, in his statistics, has mentioned the group of cases in which the ventriculogram had confirmed the neurological findings. I take it from the summary of his experience that he does not approve of performing ventriculography in cases in which a neurological diagnosis can be reached by other means. Consequently, in future reports, there should be no ventriculography figures confirming previous neurological diagnosis.

Dr. Grant: I think in the present state of ventriculography, that I should not advise it in cases where a neurological diagnosis can be made. I think you should operate upon the patient first on existing neurological evidence and resort to ventriculography only if the operation fails to reveal the neoplasm.

Dr. Pollock: How many cases are included in Dr. Grant's own series, of which 5 or 6 died?

Dr. Grant: We have had 60 cases to date. We have had a 10 per cent mortality—five of them certainly and possibly a sixth.

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Chapter XVII

THE USE OF LIPIODOL IN CASES OF TUMOR OF THE SPINAL CORD

WILLIAM JASON MIXTER, M.D.

IN the practice of medicine we must always look more or less askance at any new form of diagnostic procedure which may carry a considerable element of danger. For this reason it is wise to weigh carefully the pros and cons for the use, in the cerebrospinal space, of a substance opaque to the *x*-ray. That the use of such a substance may well carry an element of danger is, I think, self-evident.

Lipiodol is a preparation of poppy-seed oil in which iodine has been incorporated. The iodine is not simply in solution, but is in the form of a fairly stable chemical combination. For best results the iodine content should be 0.45 gm. per cubic centimeter. The oil thus constituted should be clear and of a yellow or greenish yellow color. Brown or turbid oil has deteriorated and should not be used.

Lipiodol was originated by LaFay[1] four years ago and used by him in the treatment of epidemic encephalitis. Finding that this substance was not especially irritating to the meninges and opaque to the *x*-ray, Sicard and Forestier[2,3] injected it by spinal puncture and thereby demonstrated spinal cord compression. Feeling that such a procedure might well mark a distinct advance in the diagnosis of spinal cord tumors, Dr. J. B. Ayer and I obtained a supply of the drug and began experimenting with it before using it in the human subject.

The data presented in this paper, aside from animal experiments, have been gathered from a group of 12 cases in which lipiodol has been used. Nine of these have come under personal observation at the Massachusetts General Hospital and of the remaining 3 reported, 2 are reported through the kindness of Dr. J. B. Ayer, and one through the kindness of Dr. Donald Munro. The actual injection of lipiodol in my own cases has been done by Dr. Ayer,

Dr. Henry Viets and Dr. Hugo Mella of the Neurological Staff of the Massachusetts General Hospital.

The radiography has been done largely by Dr. J. D. Camp and the examination of the cerebrospinal fluid has been carried out by Dr. Frank Fremont-Smith. To all of these gentlemen I wish to express my deep appreciation of their help and interest.

Early Experiments with Lipiodol

In the earlier experimental work with lipiodol, a marked cellular reaction was found in the cerebrospinal fluid in cats and only with some hesitation was it used in the human subject. These findings were reported briefly[4] but the work was continued. Some less toxic substance or some substance that would move more freely and rapidly in the cerebrospinal space was also sought for, but without success.

In the experimental animals which were used, from 1 to 2 c.c. of lipiodol, which would be equivalent to a dose of 20 to 40 c.c. in man, were injected, with the result that one animal died and the others showed definite cellular reaction in the cerebrospinal fluid. As the animals that survived showed no permanent ill effects, the use of the oil was begun cautiously in patients, the dosage being from 1 to 2 c.c., the first case being subjected to injection in the lumbar sac and the patient being placed in the Trendelenberg position following injection. The radiograms taken showed the oil clearly, but it seemed to remain in irregular masses in the lumbar space and lower dorsal region. These earlier failures were thought to be due probably to the fact that the heads of the patients were not lowered sufficiently or quickly enough. The later cases and animal experiments have shown that this oil may adhere to the meninges or nerve roots in droplets or even in large masses, causing the appearance of definite blocking of the cerebrospinal canal. This "false arrest," as it is called by the French writers, was very forcibly brought to notice in one animal experiment. It was supposed that a drop of mercury placed in the arachnoid space of a cat could be rolled around as one runs mercury round the bottom of a beaker; it was a surprise, however, to find that mercury was just about as difficult to move in the cerebrospinal space as lipiodol and that it was necessary to shake the cat much as one would a clinical thermometer. Even had the mercury moved freely, it would not have been available for the human subject, owing to its toxicity. Since those earlier cases lipiodol has been injected into

the cisterna magna in cases of suspected compression of the cord, reserving lumbar injection for cauda equina lesions. It has never been attempted to outline both the upper and lower limits of the same tumor, feeling that to do so required a double dose of lipiodol and that of the two, the upper limit was the more important. Cervical and dorsal injection has not been used in this series as it was felt that cervical and dorsal puncture carries an element of danger entirely out of proportion to the added knowledge to be gained thereby.

The experimental animals, as before stated, showed a definite meningeal reaction to the injection of lipiodol. The reaction reached its height twenty-four to forty-eight hours following injection when counts of 1000 cells with a moderate increase in the protein content

FIG. 27. Lipiodol in the lumbar sac eight months after injection.

of the cerebrospinal fluid were noted. The reaction subsided gradually, and by the tenth day the cerebrospinal fluid was normal. In the one case in which the patient was punctured the day following an injection of lipiodol, a count of 900 cells was found, consisting mostly of polymorphonuclear leucocytes. This reaction had entirely subsided at the end of ten days. This meningeal reaction was also noted at operation, in 2 cases operated on twenty-four and forty-eight hours respectively after the injection of lipiodol. In both of these patients the meninges appeared somewhat

thickened and reddened and the cerebrospinal fluid seemed slightly turbid. De Martel[5] speaks of this inflammatory change in the meninges, although he does not mention the turbidity of the cerebrospinal fluid. All of the cases have had a moderate amount of headache and backache, which has disappeared after a few hours or days, and a moderate rise in temperature. Lipiodol apparently remains in the cerebrospinal canal almost indefinitely. It has been shown apparently unchanged in the lower end of the lumbar sac eight months after injection. In none of the cases has there been noted any increase in paralysis and there have been no fatalities.

Technique of the Injection of Lipiodol

It has been felt that the injection of such a substance into the cerebrospinal space should not be employed unless the possible dangers attending its use were more than outweighed by the more exact diagnosis to be obtained. For this reason the technique has been modified as time went on with that end in view. It is felt that there can be no true arrest of lipiodol in the subarachnoid space in the absence of spinal subarachnoid block as demonstrated by Ayer's technique, and for that reason its use has been advised against unless block has first been demonstrated. Suspected lesions of the lower cauda equina are, of course, excepted. In order to fulfill these requirements and to permit all the necessary punctures to be performed at one sitting, a definite routine has been adopted which so far has seemed satisfactory. It is sometimes the case that these patients have had the presence of block demonstrated before their admission to the hospital. If so, the steps necessary to prove that fact are omitted.

The suspected level of cord compression is localized as closely as possible by neurological examination and radiograms taken centering at the suspected level. Should these plates be positive, as, for example, in malignant disease of the vertebrae, the use of lipiodol would usually be considered unnecessary; if negative, the patient is prepared for combined cisternal and lumbar puncture. Lumbar puncture is performed, pressure readings taken, jugular compression done and the fluid rapidly examined for protein with the needle in situ. If there is no suggestion of block, nothing further is done. If block is proved or suspected, the cisterna magna is punctured with the lumbar needle still in place. The presence or absence of block is confirmed and if block or partial block is present, the lumbar needle is withdrawn and 1.5 c.c. of lipiodol

injected into the cisterna magna, care being taken that the oil is not broken up into globules in the syringe by water or air. The patient is then sent to the x-ray room in the prone position, fluoroscoped to locate the oil and then put in the sitting position. In the future the procedure advocated by Laplane[6] should be followed; i.e., the injection is made in the x-ray room with the patient in the inclined position. Radiograms are taken at once and usually repeated in a few hours and again the next day. Occasionally plates are taken forty-eight hours after injection. Both anteroposterior and lateral views should be taken.

FIG. 28. Cisternal injection. Note partial cap above a cervical neurofibroma.

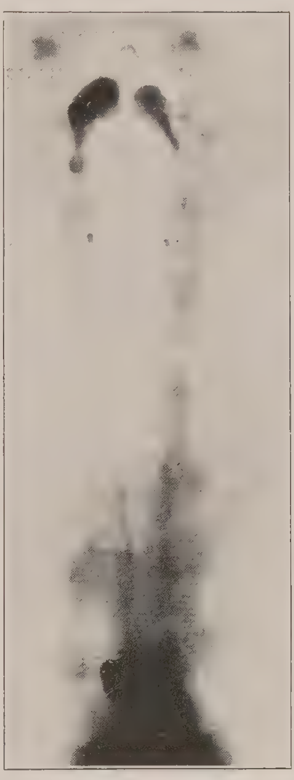

FIG. 29. Cisternal injection. Arrest in upper dorsal region. Note cap above a neurofibroma. (*Kindness of Dr. J. B. Ayer.*)

The interpretation of the films is of great importance. In the first place, the lipiodol occasionally tends to move slowly and even to stop and pile up in the canal for a short time. Such temporary arrest is of little or no significance and seems to be due to adherence of the oil to the walls of the canal or to the nerve roots. In the

experience of the authors, rounded masses of oil sticking irregularly in the canal for a few hours are of no significance. The shape of the oil shadow, particularly its lower border, is important. A cap or crescent, whether complete or incomplete, has meant, in our few cases, extramedullary tumor or Pott's disease with intraspinal abscess, while narrow lines of lipiodol at either side with an irregular mass above suggest a fusiform enlargement of the cord itself.

Lipiodol has been injected by lumbar puncture in 2 cases of suspected cauda equina tumor. The injection was satisfactory but showed irregularities that it was impossible to explain at that time. Exploration failed to reveal any tumor. It is believed that the error was due to lack of knowledge in the reading of the radiograms and that the method, after a little experience with positive cases, should be accurate and satisfactory. Epidural injection has not been used intentionally, though in one patient very good extradural radiograms were obtained accidentally, probably on account of extravasation through the needle hole.

Fig. 30. Cisternal injection. True arrest above an intraspinal abscess in dorsal region.

Effects of Lipiodol

Partial review of the literature of this subject shows that following Sicard and Forestier's paper announcing the procedure, the use of lipiodol was taken up in France, but for some time little use was made of it elsewhere. In the French literature there have been numerous reports of isolated cases and groups of cases and also a good deal of discussion from which valuable information may be gleaned. There are also a moderate number of reports to be found in the English, American and German literature. Recently Laplane,[6] working apparently in M. Sicard's clinic, has gathered together the French reports, grouped the cases and published a monograph, which is the first really authoritative statement that has appeared concerning this subject. His deduc-

tions are based on the study of 300 cases, a far larger series than any one else has had the opportunity to observe.

In the whole series no report of a fatality or of increase in paralysis can be found following the use of lipiodol. Laplane[6] reports that the injection is usually painless, though in some cases there may be root pain in the vicinity of the tumor, and that the reaction in the cerebrospinal fluid is very mild. This opinion is also held by Sicard, Forestier and Laplane,[7] and others. The removal of the oil at operation has been attempted, but without much success. It

FIG. 31. Lumbar injection. Patient inverted. False arrest. Note absence of cap.

is possible that the irritant action which has been noted by us has been due to deterioration of our supply of lipiodol, though there is no evidence of it on inspection. Sicard, Haguenau and Laplane[8] warn that it is important to allow six days to elapse after spinal puncture before lipiodol is injected. I think this point is well taken on account of the danger of cerebrospinal fluid leakage through the puncture in the dura with narrowing of the cerebrospinal space. It is not felt, however, that the removal of a small amount of fluid at the time of injection is an important

factor; it has been done habitually in these studies with no bad results.

No mention of the proof of spinal block before injection of lipiodol, which is considered an important part of the technique, has been found in the literature and no mention of true arrest of lipiodol in the absence of block has been discovered. M. Babinski[9] suggests a doubt as to the value of the procedure in all cases when he asks whether compression may occur even if normal descent of the oil is noted. Elsberg,[10] in a letter of recent date, suggests that in cases of tumor with absence of block this very thing would happen. There is no doubt that occasionally, with small tumors or those rare destructive new growths that cause narrowing of the cord, block may be absent. Such a condition has been observed three times.

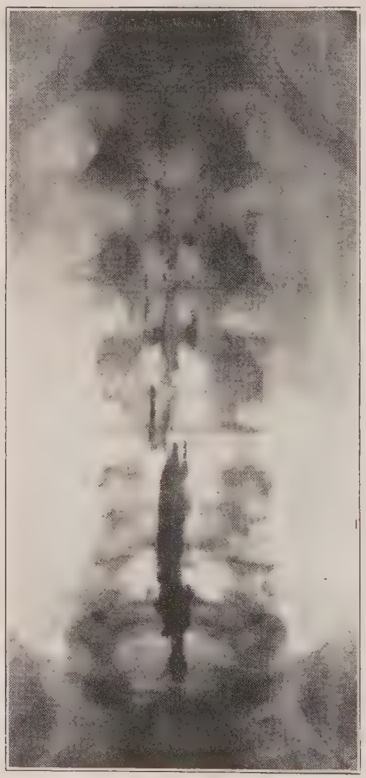

Fig. 32. Lumbar injection. Lipiodol in lumbar space. No tumor found at operation.

Concerning the ultimate fate of lipiodol in the spinal canal little is known. There are no reports of late ill effects, but the photograph of an autopsy specimen, a cyst, obtained eleven months after injection and published by Laplane,[6] is sufficient to give much food for thought. Such a cyst involving the cauda equina might well give symptoms.

Value of Lipiodol as an Aid to Diagnosis

Considerable evidence is found as to the accuracy of diagnosis by lipiodol. As well as those authors already mentioned, Sargent,[11] Ironside and Shapland,[12] Souques, Blamoutier and de Massary,[13] Foix,[14] Russell,[15] Grant,[16] Naffziger,[17] Prusik and Volicer,[18] and others agree that localization in their hands has been accurate

and satisfactory. Vincent[19] suggests that epidural injection may be more delicate in extradural lesions when he cites a case of Pott's disease in which epidural lipiodol was arrested, while that injected into the subarachnoid space descended freely.

The interpretation of the radiograms is carefully studied by Laplane.[6] He feels that false arrest can be differentiated from true arrest by the shape of the shadow and by its fixation. In true arrest the lipiodol stops because it reaches an obstruction and reversal of the position of the patient will cause the oil to flow backward away from the tumor. In false arrest the mass of oil has become fixed by adherence to the meninges and nerve roots and will not move on reversal of the patient.

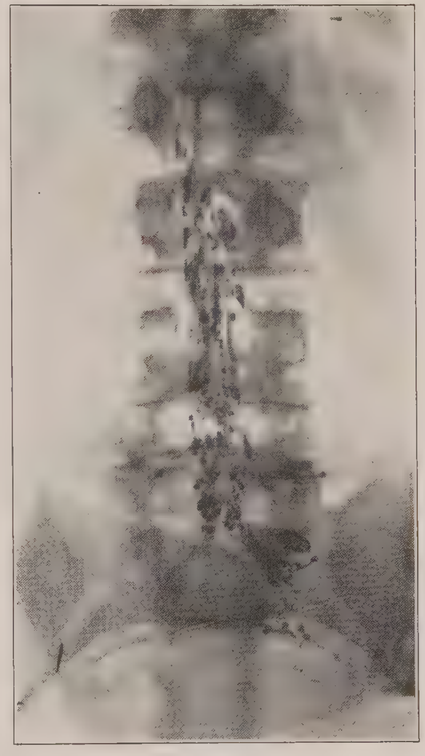

FIG. 33. Same case as Fig. 32. Plates taken twenty-four hours later. Note that most of the lipiodol has leaked out of the spinal canal and is now present in the epidural space.

How much reliance can be placed on lipiodol localization? De Martel[20] in his discussion speaks of 4 cases of arrest of lipiodol operated on by him in which no tumor was found and nothing to indicate why the lipiodol was arrested. He cites 2 of these as cases in which the lipiodol examination was the only real reason for operation and a third as one that had not had a careful neurological examination. Whether these cases would have shown spinal block by combined puncture is undetermined. De Martel feels, however, that one can localize spinal cord tumors very exactly by the use of lipiodol, but only if already so diagnosed clinically. When there is failure of accordance between the clinical and lipiodol

localization, the former will be the most reliable. However, the subject cannot be dismissed in this manner. There are too many factors involved and far too much variation in these factors. The author would state his opinion as to the diagnostic value of lipiodol as follows:

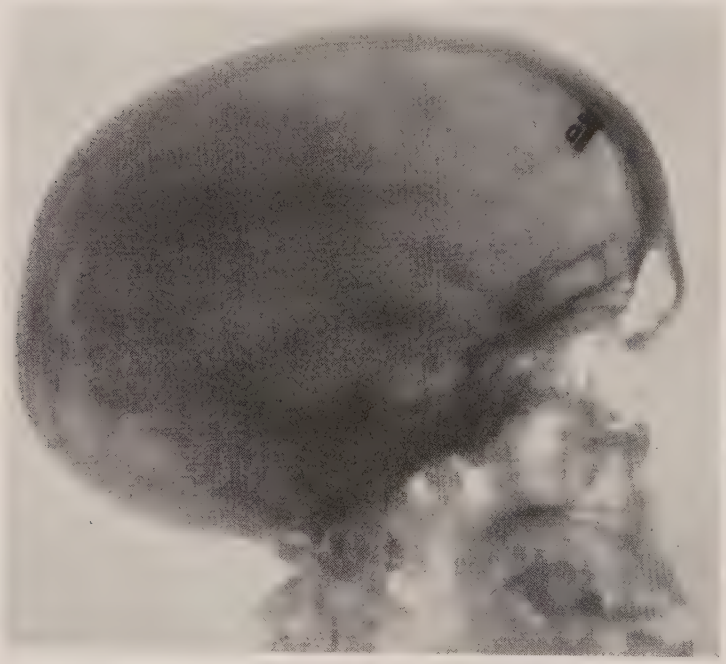

Fig. 34. Cisternal injection. Lipiodol has passed upward through the foramen magnum and has remained inside the skull. (*Kindness of Dr. Donald Munro.*)

Given evidence of block, a sharp neurological level and an indefinite lipiodol level, one would better depend on the neurological evidence.

Given a sharp localizing picture with lipiodol and a neurological level perhaps two or three segments below the level indicated by the lipiodol, one would better depend on the lipiodol level. This was the situation in one of my own cases, the tumor being found three segments above the neurological level and accurately localized by lipiodol.

Conclusions

The results which have been obtained with lipiodol in conjunction with the previous knowledge of spinal subarachnoid block suggest the following summary:

This oil is known to be somewhat irritating to the meninges from its effects on the spinal fluid, even though no immediate ill effects have been reported. It is also known that the oil remains in the subarachnoid space almost indefinitely, where it acts as a foreign body. It is felt strongly that a non-absorbable substance of this character should not be used in the spinal subarachnoid space except where definite good is to be expected from its use.

If there is no evidence of block, the oil will find nothing within the canal to stop it and injection will be useless. If accurate localization can be made by neurological examination and the presence of block is demonstrated by puncture, it is again useless. It must be remembered, however, that exact localization is difficult in the extreme in some cases. Laminectomy is a severe operation and if the exposure can be limited to three or four arches, the operative shock is less, as is also the resulting weakening of the spinal column.

Following this line of reasoning the conclusion has been reached that lipiodol will be used in all patients belonging in the class in which block has been proved and in which the level is in the slightest doubt. Lipiodol must be accepted as a definite aid in the study of spinal cord compression and the intelligent use of this material should be encouraged in a considerable percentage of tumor suspects if they are to receive the benefit of exact localization.

By combining demonstration of spinal subarachnoid block and the careful use of lipiodol, it should be possible to increase very definitely the successful removal of cord tumors and at the same time to put ourselves in a position to make a positive diagnosis of tumor and to advise laminectomy earlier in the course of the disease. Also, because of sharper localization, our operative mortality should be less.

It should be remembered that the use of lipiodol is like the Wassermann test in syphilis, the basal metabolism in goiter and a hundred other new diagnostic tests. None of these tests is sure and all of them will fail to aid if the fundamental basis of all diagnosis, the physical examination of the patient, be neglected.

Discussion

The following questions submitted to Dr. Mixter before the Commission, together with the answers to them, are here reported verbatim.

Dr. Strauss: If Dr. Mixter fears the danger of lipiodol remaining in the lower part of the dural sac why does he think it impossible to remove it by lumbar puncture?

Dr. Mixter: I do fear the danger of lipiodol remaining in the lumbar sac although there are no untoward effects reported. I think it would be extremely difficult, if not impossible, to remove the oil for two reasons: (1) on account of the fact that the oil becomes fixed to the arachnoid within a few days and (2) on account of its position in the lumbar sac, the larger part of it being below a lumbar puncture and only approachable by sacral puncture.

Dr. Spiller: Has Dr. Mixter had any serious symptoms in any case?

Dr. Mixter: We have had a certain amount of fever in about half the cases. Most of them have had headache or backache for a day or two. We have had no increase in paralysis at any time, and we have had no serious results.

Dr. Spiller: Is iodipin of the same chemical substance as lipiodol?

Dr. Mixter: I think it is, although I am not sure. The lipiodol which we have had may possibly have undergone a certain amount of deterioration. This is doubtful, however, as we have had several importations and the reaction has been similar in each shipment.

President Timme: How long did lipiodol remain in the cats that you experimented upon?

Dr. Mixter: As long as we had the cats.

President Timme: There is no diminution at all?

Dr. Mixter: Apparently not.

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Chapter XVIII

THE DIAGNOSTIC VALUE OF ROENTGENOGRAPHY

In Brain and Cord Affections Following the Simultaneous Air Displacement of the Cerebrospinal Fluid by the Spinal Puncture Method

F. LIBERSON, M.D.

THAT pneumoventriculography is an aid in diagnosing brain tumors is no longer questioned even by the most conservative, but its adoption as a routine diagnostic procedure in doubtful cases of brain tumor has not yet met with popular approval. The deterrent to its adoption is the apparently hazardous character of the procedure.

Realizing the need for a diagnostic method applicable to the doubtful and early cases of brain and cord lesions, the author was stimulated to work on a less hazardous procedure of pneumoventricular visualization than the trephine method. For this purpose a spontaneous displacement apparatus* was devised which tends to keep the intracranial and intraspinal pressures at the original balance (as was shown by cadaver and animal experimentation) during the entire period of the substitution of air for the cerebrospinal fluid by the lumbar puncture route. The apparatus, if properly used, enables one to perform a spinal puncture, even on posterior fossa tumors, because it permits only 4 c.c. of fluid to drain out of the spinal canal before an equivalent quantity of air takes its place, and, therefore, preserves the balance of the intracranial and intraspinal pressure.

There is another advantage in the spinal method of pneumography; namely, the filling of the subarachnoid space, which is of additional diagnostic value in localization of early cases of brain tumor.

The application of the spinal method of ventriculography has been extended in our hospitals to include not only cases of brain tumors, but other affections as well. (See Figs. 35–42.)

* Liberson, F. Apparatus for simultaneous displacement. *Arch. Neurol. & Psychiat.*, Chicago, 1924, xii, 300.

Case 1. W. H. Aged thirty-eight. (11127.) No. 21.

Admission Diagnosis. Meningitis. Tuberculosis suspected.

Duration of Illness. Three weeks.

Roentgenogram. (Figs. 35 and 36.) Taken for the purpose of determining the patency of the foramina which connect the ventricles and the subarachnoid spaces.

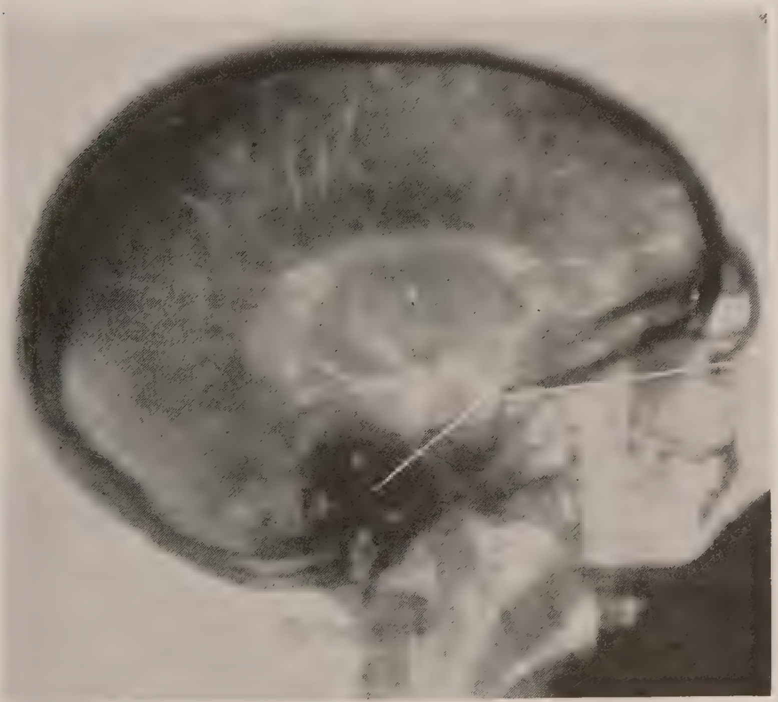

Fig. 35. Case of cerebrospinal lues (lateral view). Communication is present between the ventricles and the subarachnoid spaces, the ventricles are filled and normal in outline and the sulci are well filled all over the brain.

Findings. Communication is present between the ventricles and the subarachnoid spaces. The ventricles are found to be filled and normal in outline, and the sulci are well filled all over the brain. The clinical diagnosis is changed from meningitis, which is possibly tuberculous, to that of cerebrospinal lues.

Treatment. Antiluetic intravenous, with complete drainage and simultaneous air substitution of the spinal fluid by the spinal route. Patient discharged, improved.

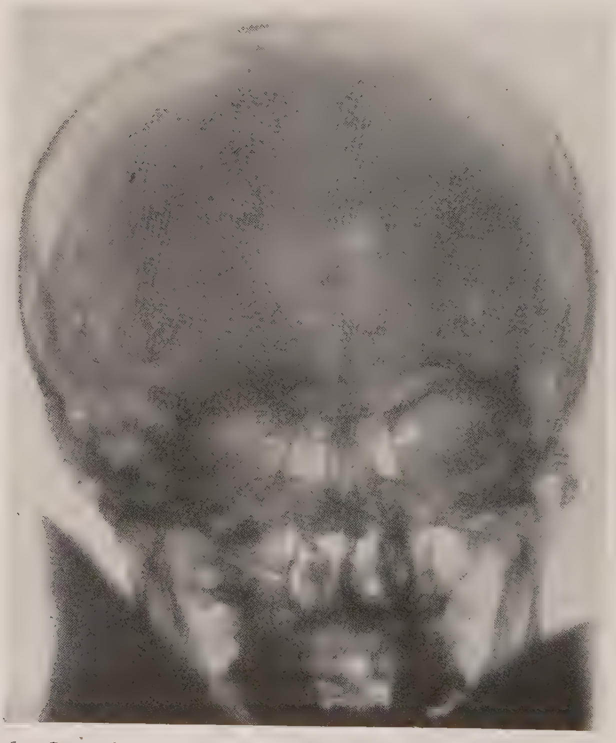

Fig. 36. Case of cerebrospinal lues (front view). Communication is present between the ventricles and the subarachnoid spaces, the ventricles are filled and normal in outline and the sulci are well filled all over the brain.

Case II. C. A. Aged fifty-three. (10644.) No. 21.

Admission Diagnosis. Tabes dorsalis.

Duration of Illness. Seven months.

Roentgenogram. (Fig. 37.) Taken with the patient in the erect posture, during the course of the therapeutic drainage of the cerebrospinal fluid and air replacement.

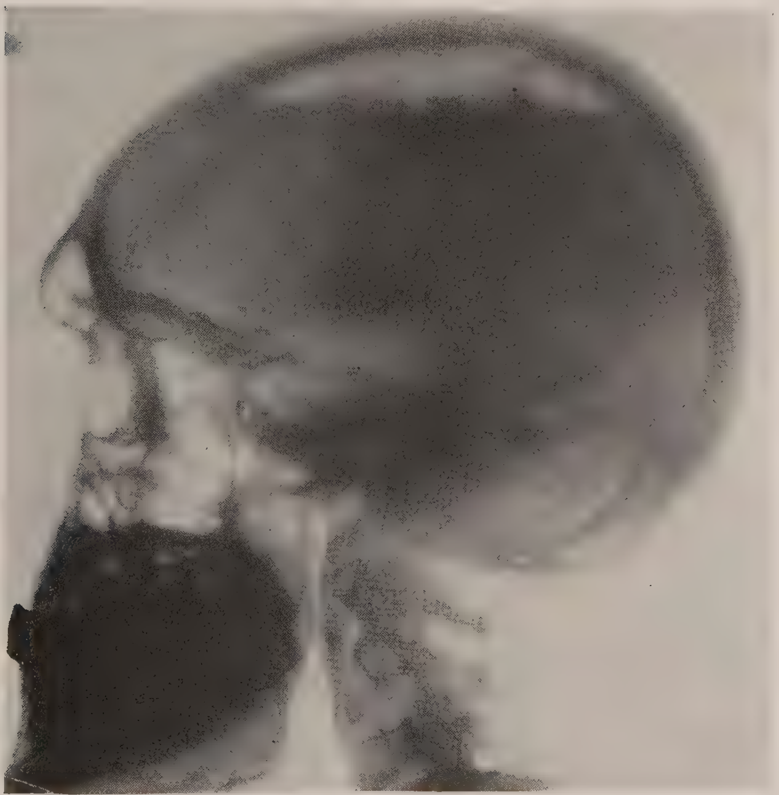

FIG. 37. Case of paresis. There is absence of outline of the sulci, and collection of air at the dome, suggesting a retracted brain.

Findings. There was absence of outline of the sulci and there was also collection of air at the dome; these findings were very strongly suggestive of a retracted brain.

Treatment. As in Case I. Patient discharged with diagnosis of paresis, condition improved.

Case III. H. A. Aged thirty-seven. (10431.) No. 21.

Admission Diagnosis. Right hemiparesis, cerebrospinal lues.

Duration of Illness. Not known.

Roentgenogram. (Figs. 38 and 39.) Taken during the course of the therapeutic drainage of the cerebrospinal fluid and the replacement of the fluid with air.

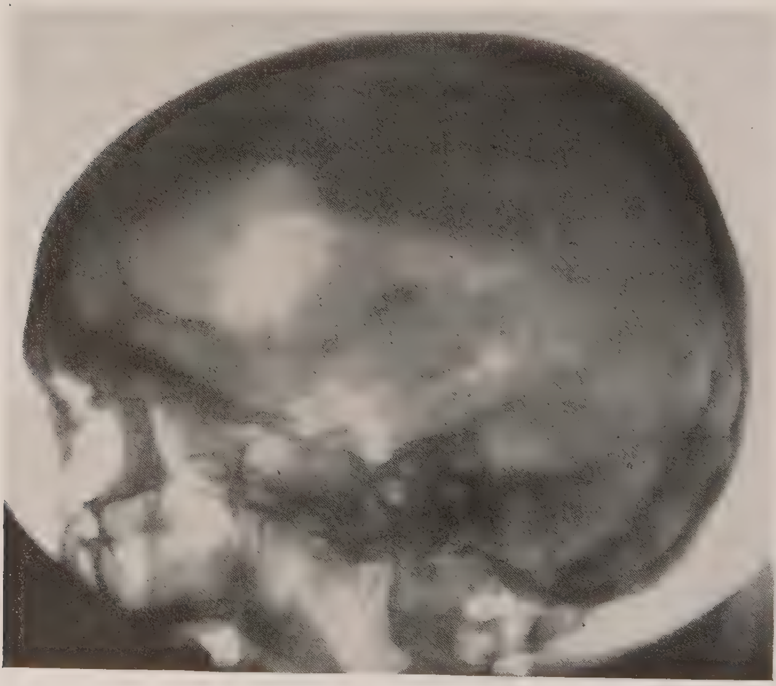

FIG. 38. Case of syphilitic meningoencephalitis. There is marked enlargement of the anterior horn of the left lateral ventricle. The right lateral ventricle is slightly enlarged, suggesting an obstruction.

Findings. Marked enlargement of the anterior horn of the left lateral ventricle. The right lateral ventricle is also slightly enlarged, suggesting an obstruction.

Treatment. As in Case I. An operation was advised but not urged as the condition of the patient improved. The patient was discharged at his own request. The diagnosis at the time of discharge was that of syphilitic meningoencephalitis.

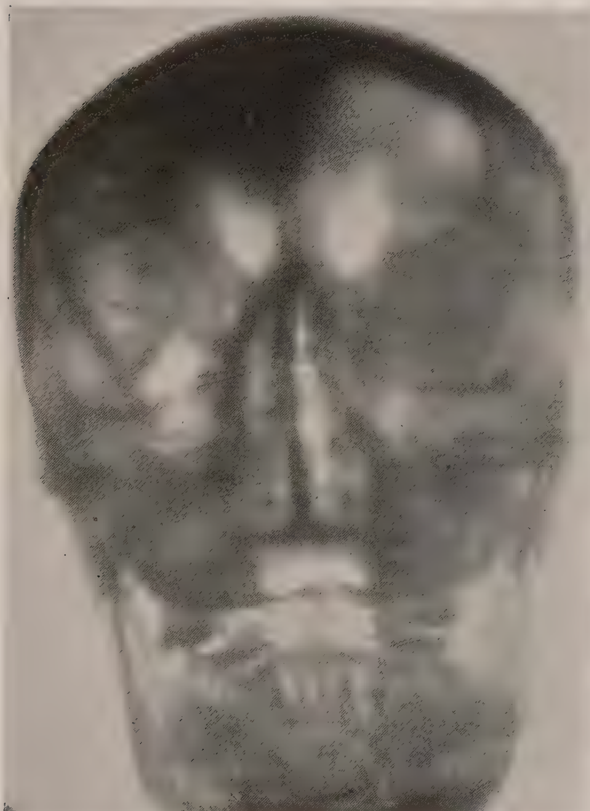

FIG. 39. Case of syphilitic meningoencephalitis. There is marked enlargement of the anterior horn of the left lateral ventricle. The right lateral ventricle is slightly enlarged, suggesting an obstruction.

Case IV. B. T. Aged twenty-eight. (11924.) No. 21.
Admission Diagnosis. Paraplegia.
Duration of Illness. One week.
Roentgenogram. (Fig. 40.) Taken to exclude neoplasm.

FIG. 40. Case of paraplegia. There is no obstruction to the free communication between the ventricular and subarachnoid systems, and there is no interruption of the air lines on both sides of the cord up to the cisternae.

Findings. No obstruction to the free communication between the ventricular and subarachnoid systems; the air lines are not interrupted on both sides of the cord up to the cisternae.

Treatment. As in Case I, but no improvement up to the present time (three months).

Case v. W. B. Aged twenty. (9578.) No. 21.
Admission Diagnosis. Paraplegia, spinal pachymeningitis.
Duration of Illness. Eight months.
Roentgenogram. (Fig. 41.) Taken to determine and locate spinal lesion.

FIG. 41. Case of paraplegia, spinal pachymeningitis. There is imperceptibly gradual diminution of the air shadow on both sides of the cord from the tenth up to the eighth dorsal segment, with no air above the eighth dorsal segment, a condition suggesting adhesions.

Findings. Imperceptibly gradual diminution of the air shadow on both sides of the cord from the tenth dorsal up to the eighth, with no air above the eighth dorsal segment, suggesting adhesions.

Treatment. Antiluetic for six months, no improvement. Operation with separation of adhesions. Patient was discharged completely recovered.

Case VI. A. R. Aged twenty-two. (1892.) No. 70.
Admission Diagnosis. Cord tumor.
Duration of Illness. Six weeks.
Roentgenogram. (Fig. 42.) Taken to determine the location of the tumor.

FIG. 42. Case of extradural tumor. The air shadows curve on both sides of the cord beginning at the ninth thoracic segment and extending on the right side to the upper border of the eighth thoracic segment. There is no air above the level of the eighth dorsal segment, a finding which suggests the lowest situation of the tumor.

Findings. Curving of the air shadows on both sides of the cord beginning at the ninth thoracic segment and extending to the upper border of the eighth thoracic segment on the right side, with no air above the level of the eighth dorsal segment, suggesting the lowest situation of the tumor.

Treatment. Operation with removal of an extradural tumor about 5 cm. in length. Patient was discharged completely recovered.

Summary and Conclusion

1. The simultaneous cerebrospinal fluid replacement by air through lumbar puncture can be used in various cerebrospinal affections. It was used in 20 cases and in several cases as many as six times with no ill effects.

2. This method of visualizing the ventricular and subarachnoid systems, if properly done, has no more hazards than an ordinary spinal puncture, and the information, if properly correlated, is quite often conclusive and decisive.

I take this opportunity to express my gratitude to Dr. C. H. Lavinder, Surgeon in Charge, U. S. Marine Hospital No. 21, and to Dr. E. K. Sprague, Surgeon in Charge, U. S. Marine Hospital No. 70, for their permission to use the clinical records herein presented.

Section V

CHANGES IN THE HUMAN CEREBROSPINAL FLUID IN CONNECTION WITH DISEASES OF THE CENTRAL NERVOUS SYSTEM

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Chapter XIX

THE REACTION OF THE HUMAN CEREBROSPINAL FLUID IN INFECTIOUS INFLAMMATORY CONDITIONS OF THE MENINGES (MENINGITIS SYMPATHICA)

ISRAEL STRAUSS, M.D., AND DAVID J. KALISKI, M.D.

IN acute inflammation of the meninges there is always more or less damage to the secreting mechanism of the cerebrospinal fluid, the chorioid plexus, as well as to the cells of the membranes and to the blood vessels. As the cells of the chorioid plexus are chiefly responsible for the exact composition of the fluid as well as for the rate of secretion, in acute inflammations of the meninges there are profound changes in the composition of the fluid as well as in its rate of secretion. In addition, the fluid contains the products of acute inflammatory changes in the membranes and occasionally in the adjoining brain and spinal cord tissue. On account of over-secretion of fluid with possibly damage to the absorbing mechanism through the arachnoidal villi into the venous sinuses of the skull, there is always increased pressure. It is known that in health practically no antibodies can be detected in the fluid by the ordinary biological reactions. The various ferments are absent. Complement and hemolysin are not detectable. Agglutinins are practically never demonstrated. It is questionable whether the fluid has any definite bactericidal action. But in diseases of the membranes, especially acute inflammatory disease, the efficient barrier of the chorioid plexus is penetrated, and no doubt the inflamed membranes, together with engorged and diseased blood vessels, add to the quota of immune substances then found in the fluid. Complement fixing bodies, hemolysins, agglu-

tinins and ferments then find their way into the fluid and can be detected by suitable tests. Again, in health the plexus acts as a barrier to the entrance of most drugs given orally or parenterally. We have shown that arsenic can pass the barrier only in minute quantities in health, or at least where the spinal fluid shows no abnormalities. This has been corroborated by others. When the meninges are inflamed, conditions are changed, and such drugs as arsenic, iodides, hexamethylene tetramine, nitrates and occasionally other drugs, such as alcohol, pass the barrier with much greater facility and in greater concentration.

Certain substances normally present in the fluid now become greatly increased in amount and concentration. This is true of the proteins, albumin and the globulins, phosphorus and cholesterol. On the other hand, the chlorides which are normally present in greater concentration in the fluid than in the blood are diminished in amount, especially in tuberculous meningitis. Fibrinogen, normally absent, now makes its presence known by the formation of pellicles and coagula. Lactic acid and choline are increased in amount. The cells normally found in the fluid are usually of the small lymphocytic variety, with rarely an occasional endothelial cell or a broken-down cell, the result of tissue desquamation. The lymphocytes rarely exceed four to eight to the cubic millimeter, and usually are below this number. In acute inflammatory disease of the meninges, the cells are greatly increased in number, ranging from four or five all the way into the thousands, depending on the intensity and extent of the inflammation. Polymorphonuclear cells take the place of the lymphocytic variety in most instances, and, in addition, plasma cells, large phagocytic cells and cell detritus may be found. In the more purulent types of inflammation the fluid may even become frankly purulent, change in color and coagulate spontaneously, due to the tremendous amount of protein and fibrinogen present. Glucose, normally present, is altered in amount, usually being decreased and frequently is entirely absent.

And finally, the causative agents of disease, bacteria and protozoa, make their way into the central nervous system and subarachnoid space and can be detected by suitable tests. Whether organisms reach the fluid through the chorioid plexus or by direct extension from the brain or spinal cord on the one hand or the cranial bones, vertebrae, cranial sinuses or the nearby nasal or aural cavities on the other, will not be gone into here. Suffice it to

say that organisms may appear in the cerebrospinal fluid either coincidentally with or subsequent to alteration of the fluid itself.

In general, these are the changes that may be looked for in the cerebrospinal fluid in disease of the meninges and also to a certain extent in similar involvement of the underlying brain and spinal cord. The variations of the general picture and the specific differences due to the large number of invading organisms will be considered under separate headings devoted to the various types of meningeal inflammation.

Tuberculous Meningitis

The fluid is almost always under greatly increased pressure, varying from 150 to 700 or more millimeters of water. Pressure is greatest during the earliest days of the disease, diminishing toward the end. The color is usually unchanged, but with a marked increase in the number of cells. It may, however, be hazy or like ground-glass. It is rarely opalescent, bloody or turbid; and if turbid, the clouding is due to secondary infection, from caries of the vertebrae or from a mixed infection of the tubercle bacillus with the meningococcus, a few instances of which are recorded. A fine thread-like pellicle usually forms within twenty-four hours. The cytology of the fluid is fairly constant, showing a moderate increase in lymphocytes, varying from twenty or thirty to three hundred or more to the cubic millimeter. In a small percentage of the cases, perhaps 5 per cent, polymorphonuclear leucocytes may predominate throughout the disease, more commonly during the first few days or the first week of the disease, giving way to a gradually increasing preponderance of lymphocytes. Occasionally endothelial cells are present in small numbers. The globulin is slightly increased, but if blockage occurs in the canal or at a higher level, the globulin may be greatly increased. The chlorides are decreased in amount, often below 0.6 per cent per 100 c.c. of fluid. The permanganate index of Mayerhofer is slightly increased; the normal being below 2 for non-meningitic fluid, while in this disease it is close to 2.5. The inorganic phosphorus is increased to 2.54 mgms. per 100 c.c., the normal being about 1.64 mgms. per 100 c.c. The sugar content varies: in some cases it is not altered, but there may be a reduction below the normal minimum of 0.05 per cent, especially at the height of the disease. The sugar may be entirely absent. There seems to be no relationship between the amount of sugar present and the course and prognosis of the disease. The hydrogen-ion concentration is not changed.

The behavior of the fluid in regard to the colloidal reactions also varies. While there is no specific change, there may be some decolorization in the meningitic zone in the colloidal gold test, the figures being approximately 0000234410, but frequently there is no change. The chief diagnostic factor is, of course, the presence of tubercle bacilli in the fluid. If the examination is careful and is sufficiently prolonged, each fluid being examined for at least two hours, the bacilli will be found in at least 80 per cent to 90 per cent of the cases.

The morphology of the organism and its staining properties are so well known as to require no repetition here, but it is worth while to detail the method of examination in use in our laboratory, which is very successful in the finding of the organisms in a large percentage of the cases. The fluid should be obtained in as large a quantity as possible, and unless there is great urgency, should be allowed to stand until the pellicle forms. If an immediate examination is necessary, a portion of the fluid should be preserved until the pellicle forms, should the first search prove unsuccessful. The fluid is centrifuged in a high powered machine for from fifteen to thirty minutes, the supernatant portion poured off, and the remaining few drops or cubic centimeter, containing the sedimented pellicle, deposited on a large clean cover glass, the pellicle being thoroughly mixed through the fluid. This is allowed to dry in an incubator at 37°c., and is then fixed and stained in the usual way. This technique introduced by Bernstein resulted in 95 successes out of 100 consecutive examinations. Cheer has recently introduced a simple procedure which consists of the addition of one-third volume of 95 per cent alcohol to the fluid before centrifuging. This amount permits the organisms to descend to the bottom of the tube and, in addition, forms a thin albuminous cloud which helps to sweep the organisms down with it, much as the pellicle does, and at the same time fixes the cells in the precipitate. Thus the same stain can also be used for differential diagnosis. Other methods, consisting of the addition of precipitants to facilitate the deposit of the organisms, i.e., tannic acid, have also been suggested, as well as the addition of small bits of absorbent cotton to entangle the bacilli and facilitate their deposition at the bottom of the centrifuge tube. The addition of a drop of egg-white is also of help, especially in cases where the cell-bulk is very small. In the event of failure of these methods, guinea-pig inoculation may be resorted to.

It might be worth while to consider the reasons for failure to find bacilli in certain fluids obtained from definitely proved cases of tuberculous meningitis. First, the process may be definitely localized, as described by Foerster, without any change in the fluid at all. Then there may be a localized tuberculoma, with an accompanying serous meningitis or even a meningitis sympathica. In this event bacilli might not be present in the fluid. There may be a localized meningoencephalitis, as described by Oppenheim, of tubercular origin, usually occurring on the convexity, with symptoms of a focal rather than of a generalized nature and with few if any changes in the fluid. It is not infrequently observed that a tubercular or scrofulous individual may develop a serous meningitis, resembling clinically a real tuberculous meningitis but with few if any changes in the fluid beyond an increase in the pressure reading. Again, the exudate at the base may be very thick, with marked thickening and adhesion between the membranes with a walling-off of the process, the fluid below being practically unchanged; or this plastic exudate may close the foramina of exit, those of Magendie and Luschka, thus causing a block. In this event, the Queckenstedt phenomenon is absent, i.e., pressure on the jugular veins causes no increase in the flow from the needle in the lumbar subarachnoid space. Finally, there may be adhesions between the membranes in the cervical region or elsewhere along the vertical canal, with the formation of loculi, blockage below the adhesions, and the presence of a xanthochromic fluid and the other changes described in the Froin syndrome. Cases of this type have been described by Oppenheim, and by Sprunt and Walker. In the case reported by the latter, no bacilli were found in the xanthochromic fluid, which coagulated spontaneously after withdrawal, but they were found in the cerebral ventricles. In the event of spinal block cisternal or ventricular puncture may be resorted to in order to find the bacilli. If the block is situated at or above the medulla, cisternal puncture will be of no avail and ventricular puncture may then have to be performed.

Meningococcus Meningitis

In meningitis due to infection by the meningococcus, the pressure and amount of the fluid are always increased. A low pressure or the absence of the Queckenstedt phenomenon should make one suspicious of a partial or complete block. The pressure reading is usually from 200 to 800 mm. of water. The fluid is usually already turbid at the time of the first puncture and of a yellowish-green or grayish

color. As the disease progresses, the sediment of pus increases and may be very thick and granular in type. The protein is greatly increased above normal and may reach as high as 6 gms. per 100 c.c. A thick pellicle forms soon after withdrawal. The glucose content is promptly reduced and soon is absent altogether. As the infection recedes, it gradually reappears. The chlorides are only slightly reduced in amount and the phosphates are increased. The hydrogen-ion concentration is increased and the alkali reserve reduced. The permanganate organic index is greatly raised, to 5 or 6. The cells in the fluid are greatly increased in number, usually to thousands, and are practically all of the polymorphonuclear variety. A few lymphocytes, endothelial and plasma cells and cell detritus are found in smears. If the puncture is performed late in the disease, there may be less marked changes, especially if the infection is declining. It must be borne in mind that the frequent administration of antimeningococcus serum may cause irritation of the meninges with marked cellular response, even though the number of organisms in the fluid is declining or entirely absent. The changes determined by the colloidal reactions are marked and characteristic. With the colloidal gold test one finds almost complete decolorization or precipitation in the seventh and eighth or sixth, seventh and eighth tubes, the test reading as follows: 00002344200 or 0000245520. This is the typical meningitic curve or the "Verschiebung nach oben" of the Germans.

Finally, the specific organism of the disease, the meningococcus of Weichselbaum, in its various forms and types, is found in smears and cultures of the fluid. The characteristics of this intra- and extracellular Gram-negative diplococcus are so well known that it is unnecessary to describe them further here. Frequently the germs are present in very small numbers in the first few days of the disease; occasionally they may be entirely absent in both smears and cultures on the first examination, even after prolonged search and in the presence of definite clinical symptoms. Occasionally, while present in smears, they will not grow on the ordinary culture media. On account of the thickness of the exudate, there may be a block either within the cranial cavity or somewhere along the vertebral canal, with either no change in the fluid or with the changes described above which are due to loculation with xanthochromia and spontaneous coagulation. In a few instances already described there has been a combination of this organism with the tubercle bacillus, but these cases are very rare.

In meningococcus meningitis especially, a thick plastic exudate over the medullary exits of the subarachnoid space may cause a block with clear fluid below; and in the course of the disease, puncture may give only a small amount of fluid because of the formation of this blockage. Ventricular puncture may have to be resorted to for diagnosis. It may be pointed out that if the organisms are scarce, they may be mistaken for pneumococci, and cultural and even biological methods may have to be carried out for diagnosis. During the past year, it may be interesting to know, there has not been a single case admitted to the hospital in which the meningococcus was isolated from the fluid. It seems that in some instances the pneumococcus has been mistaken for the meningococcus on account of the occasional morphological similarity, especially to the inexpert examiner. A Gram stain should be done on each specimen before the routine cultural tests for definite diagnosis are resorted to.

Pneumococcus Meningitis

This is an acute type of meningitis with spinal fluid findings similar to those described above, except that the pneumococcus instead of the meningococcus is found in the fluid. The fluid is usually turbid and flaky and of a dirty grayish color. The pressure is increased greatly, the proteins greatly in excess, the sugar reduced or absent and the cells increased into the thousands. This type particularly has a tendency in rare instances to the formation of a thick exudate without any change in the pressure. The bacteriology of the fluid shows the presence of the pneumococcus, encapsulated and Gram-positive, and biological tests may reveal the presence of any of the four types of the organism.

Miscellaneous Types of Meningitis

This group comprises organisms responsible for an intense inflammation of the meninges. Among these may be mentioned the Streptococcus hemolyticus, Streptococcus viridans, staphylococci of various types, the colon bacillus, the typhoid bacillus, the Bacillus pyocyaneus, the influenza bacillus, the Streptococcus mucosus, the Bacillus mucosus capsulatus, the gas bacillus and the gonococcus. Among organisms causing meningitis of a less virulent type may be mentioned the yeasts, streptothrix, trichinae and actinomyces. These organisms invade the meninges from adjacent foci of inflammation and suppuration in the bones of the skull or in the brain or in the sinuses of the skull; or from the

ear, from infected blood vessels or from trauma to the skull with infection, arising spontaneously or as a result of surgical interference. The infection may also be carried to the central nervous system by the blood or lymph stream. These types are occasionally found without a definitely ascertainable primary focus elsewhere and must then be considered as primary infections of the meninges. Examination of the cerebrospinal fluid is of the greatest importance in the diagnosis of meningeal infection when symptoms of meningeal irritation arise in the course of an infectious disease, for example, typhoid fever; or following the various ear, eye, nose or sinus involvements or operations on these structures. The result of the cerebrospinal fluid examination tells us whether we are dealing with either a pseudomeningitis or a real inflammation.

Under the first heading may be classed the conditions known as meningism and serous meningitis, but not meningitis sympathica, which will be considered later, or aseptic meningitis, the result of irritating injections into the subarachnoid space. In children one not infrequently encounters types of meningitis or meningeal irritation due to ascarides, autointoxication or gastrointestinal upsets. Meningitis may also be present in the course of or following epidemic parotitis. All of these conditions require differentiation by examination of the spinal fluid. One can dispose of these latter conditions by saying that the spinal fluid may be under increased tension, but otherwise there is no change from the normal, excepting an occasional moderate increase in the lymphocytes. In some instances there may be twenty, thirty or even more cells, but the fluid is clear, and no organisms are found. When the fluid is cloudy or turbid, we are dealing with infection caused by one of the organisms first mentioned. A cloudy or turbid fluid without organisms, especially in the presence of a focal infection, should make us suspicious of meningitis sympathica, or, in the absence of the Queckenstedt phenomenon, of blocking of the canal.

Pyogenic Streptococcus Meningitis. The various types of streptococci produce a cloudy or purulent spinal fluid, with all the changes described in the other types of purulent inflammation of the meninges, together with the presence of one of the types of streptococci mentioned. Even the less virulent type of Streptococcus viridans may give a very purulent fluid; but, on the other hand, the infection may be seemingly mildly virulent, going on to recovery.

Colon Bacillus Meningitis. In colon bacillus infection the fluid is very turbid, and of a brownish or yellowish color. The fluid has the characteristics of the other purulent types, with the presence in the fluid of the slightly motile, Gram-negative, acid- and gas-producing bacillus known as the colon bacillus. Polymorphonuclear leucocytes predominate in this type of meningitis which must be differentiated from the purulent type of meningitis caused by the typhoid bacillus and by the Bacillus mucosus capsulatus. In typhoid infection the fluid possesses the same changes as in the colon type infection, but there is a more frequent predominance of the small lymphocytic type of cell. The more actively motile typhoid bacillus is found in the purulent fluid. In addition. the fluid is found to respond to both agglutination and complement fixation tests with the typhoid bacillus as antigen. While this type is uncommon, more than 35 cases have been cited in the literature The Bacillus mucosus capsulatus is a rare infection, and the organism is determined by the presence of a capsule and by the sugar reactions.

Anthrax Bacillus and Gonococcus Meningitis. The anthrax bacillus has been isolated from the spinal fluid in rare cases of this type of infection. The gonococcus has also been described as occurring in the fluid. The fluid possesses no special characteristics, and the diagnosis depends on very accurate bacteriological tests for the differentiation of the gonococcus from its morphologically similar prototype, the meningococcus, and more particularly upon agglutination, precipitation and complement fixation tests.

Influenza Bacillus Meningitis. Influenza meningitis is not very rare. The general characteristics of the fluid are not essentially different from those found in the other acute inflammatory types. There may be a predominance of the small lymphocytic type of cell, but the diagnosis rests upon the detection in the turbid fluid of the small, Gram-negative, hemoglobinophilic bacillus. It was thought that the influenza bacillus was the only organism that caused the formation of indol (Rivers), but at present this is not believed to be the case. In an active hospital service the presence of a case or two of this type of meningitis in the course of a year is to be expected.

Meningitis of Parotitis. Preceding, during or following epidemics of mumps, either in adults or more frequently in children, a type of meningitis is found which clinically resembles the

acute, purulent types, but which on spinal puncture gives a clear fluid, under increased pressure, without other changes excepting a moderate or slight increase in cells, usually of the lymphocytic variety. These cases may be very sick, and resemble very closely the epidemic types of meningitis from which they can only be differentiated by lumbar puncture and examination of the fluid.

Malignant Edema Meningitis. In a case described by Raab the bacillus of malignant edema was found both in the blood and the cerebrospinal fluid of a case that suddenly developed headache, weakness, vomiting and other signs of meningitis. This organism was found, but the case went on to recovery on the twentieth day of the disease. In other cases in the literature the infection could be explained by a secondary invasion from an old otitis or by cranial trauma.

Streptothrix Meningitis. In a number of cases on record, the streptothrix was found present in conjunction with the tubercle bacillus. A fatal case of this type of infection has been described by Neumann, Rabinowitsch and Kempner.

Yeast or Primary Blastomycotic Meningitis

This is a very rare type of meningitis, which may come on fairly rapidly, but which usually presents the more insidious onset of tuberculous meningitis from which it must be differentiated. On account of the close resemblance of this type of infection of the meninges to the tuberculous type, it is quite possible that a fair number of cases of yeast meningitis have masqueraded as tuberculous meningitis in which the organisms could not be found.

The bibliography of this form is very meager. A case was reported in this country by Shapiro and Neal[1] and a second case by D. L. Barlow[2]; another case is reported by Türk.[3] These cases are seldom diagnosed during life. Shapiro and Neal's case was a boy sixteen years old who developed a severe headache after eating chocolate on May 15, 1923. The headache persisted for a number of days, vomiting ensued and he was sent to a sanitarium. A papilledema developed. The temperature was normal. Excepting for a few hours of delirium, the mentality was clear. The blood count showed a leucocytosis with a marked polynucleosis. The back of the neck was tender, but there was no well defined stiffness. A moderate Kernig was present. Indefinite complaint of a disturbance of vision was made. The spinal puncture showed the fluid to be under markedly increased pressure. A pathological yeast (torula) was found both by smear and culture.

The case described by Barlow as one of primary blastomycotic meningitis was probably not the first of the type, primary in the meninges, as Swift and Bull reported a case of this type in 1917, and at least two other cases were reported in Australia before this case. Barlow's case was the first in a child, and

a dog infected intraspinally with the cerebrospinal fluid of this case ran a rapidly fatal course. (The route of infection is really unknown, though Watanbi considers the tonsils the portal of entry.) The patient was a female child, three years old, admitted to the hospital with a history of four weeks' indisposition, resembling the prodromal period of tuberculous meningitis. In the hospital the child was restless, grinding its teeth, crying out at intervals, and ate only after persuasion. Unconsciousness ensued and the left side of the face twitched. The pupils were equal, moderately dilated, the Kernig was positive but the head was not retracted, though the neck was stiff. Tache cérébrale was present. The superficial abdominal reflexes and the plantar reflexes were present but the knee-jerks were absent. The temperature was 102°F. The fundi could not be examined. The spinal fluid was under increased pressure and was clear. The lymphocytes were increased. No organisms were found on smear or culture. The child was once again punctured, with the same findings. A month after admission the clinical condition described became worse, the legs being curled up and the back stiff. Two months after admission a lumbar puncture was again performed and a cloudy fluid with a yellowish amorphous material was obtained. Numerous yeast cells and lymphocytes were now found and remained abundant until the child died. Before death a bilateral optic atrophy with blindness ensued. The child became increasingly more stuporous and died three months after admission. Throughout the illness the highest temperature recorded was 103°F., although it rarely went over 102°F. The post-mortem examination revealed a marked thickening of the pia with areas of brownish pigmentation about the medulla and cord which in spots were gelatinous. Microscopically yeast cells were found between the pia mater and the brain and in the interstices of the pia mater. There was also a round-celled infiltration about the vessels, together with some edema. The spinal cord showed the same changes as the medulla. The lungs were negative.

Syphilitic Meningitis

Acute syphilitic meningitis may be of rather sudden onset in an individual with recent or late latent lues. The differential diagnosis is entirely dependent upon the outcome of the biological reactions because the fluid may be clear or faintly clouded from the presence of an increased number of lymphocytes. The diagnosis is dependent upon the presence of a positive Wassermann reaction in the fluid. The increased pressure, globulin content, pleocytosis, normal sugar estimation and the outcome of the colloidal gold curve may or may not be helpful.

Meningitis with Anterior Poliomyelitis

The spinal fluid shows distinct changes in the early stages of acute anterior poliomyelitis. It is already changed during the first week, containing an increased number of cells; the pressure may be moderately or greatly increased; and, on standing, a fine, web-like clot may form. If the cells are greatly increased, the fluid,

instead of being clear, shows a ground-glass clouding. Usually there is a moderate increase in cells, up to 100 or 200, but occasionally 600 to 1000 or more to the cubic millimeter may be found. The predominating type of cell is the lymphocyte, but frequently in the early days, especially in the preparalytic stage, polymorphonuclears may predominate to the extent of 80 per cent or more. Occasionally large phagocytic cells with vacuoles are to be seen. According to Peabody, Draper and Dochez, the highest cell count is obtained in the early stage of the disease, with a gradual falling off as the disease progresses. The globulin is usually slightly increased during the first week, gradually increases in amount during the second and third weeks and may persist long after the acute symptoms have passed away. Out of 69 cases studied by these authors, only 2 cases showed normal fluids.

Bacteriologically the fluid may be said to be negative. Organisms have been described in the fluid by Rosenow and others, but as yet these findings have not been accepted as final evidence of the etiological relationship between the bacteria found and acute poliomyelitis. Chemically, aside from the slight increase in globulin, the fluid shows no change from the normal. Complement-fixing bodies have not been demonstrated in the fluid of these cases, although studies have been made both on human and animal serum by Romer and Joseph, Gay and Lucas, Wollstein, Kaliski and Strauss, and others. The results of Neustadter and Ranzhaf, in the opinion of the writer, are not conclusive of the presence of such bodies.

Early diagnosis, especially before the appearance of paralytic signs, is facilitated during epidemics by the finding of a clear or slightly turbid fluid with a marked increase in cells, the polymorphonuclear leucocytes predominating before the appearance of paralysis, and a slight increase in globulin; or by the finding of a moderate increase in the number of cells, with a lymphocytic prevalence and a slight or moderate increase in globulin. These cases, especially of the abortive type or in the preparalytic stage, must be differentiated from tuberculous meningitis, in which there is much less frequently an increase in polymorphonuclears and in which tubercle bacilli can usually be found, and from other types of meningitis. From encephalitis, especially the type known as epidemic encephalitis, poliomyelitis can be differentiated, not on any definite differences in the spinal fluids—for these may be similar—but on the prevalence of paralyses of the ocular muscles

and involvement of the base of the brain, especially the cranial nerves, combined with marked drowsiness. It is not always easy to differentiate anterior poliomyelitis in the adult from meningomyelitis of syphilitic origin. In a case of this type seen by the writer, the paralysis, occurring during an epidemic, was almost typical of poliomyelitis, but the positive Wassermann in the fluid and in the blood, together with increased cell-count and globulin, and the response to treatment left little doubt as to the true nature of the infection.

Trichina Spiralis Meningitis

The Trichina spiralis has been found in the cerebrospinal fluid by Van Cott and Lintz, in a case that resulted fatally. Among other typical symptoms of the disease, marked nervous symptoms suggestive of meningeal involvement were present, and trichinae were found in the fluid. The fluid was under moderate pressure, contained a trace of albumin and on standing showed a grayish-white sediment. Fehling's solution was not reduced. Microscopically lymphocytes and actively motile trichinae, 1 mm. in length, were observed. No parasites could be found in the blood, but the muscles contained large numbers. According to these authors, the nervous symptoms are due not only to the toxemia but also to the mechanical pressure on the brain and cord by the trichinae. Subsequently Lintz reported three additional cases. The trichinae were found to be actively motile in the fluid and kept their motility at room temperature for three days.

Meningitis Sympathica

Acute suppurative conditions, either in the accessory sinuses of the cranium or in the ear and its related structures, and in the brain, very frequently cause a reaction in the cerebrospinal fluid. This reaction is characterized (1) by an increase in the amount of the fluid; (2) by an increase in the albumin content, which may be moderate or considerable; (3) by pleocytosis, in which there is generally an increase of polymorphonuclear leucocytes, but which can occasionally be due to an increase in the number of lymphocytes; and (4) by a turbidity of the fluid.

These changes in the fluid may be associated with the symptoms of meningitis, such as rigidity of the neck and the presence of Kernig's symptom. This reaction has been given the name of meningitis sympathica by Plaut, Rehm and Schottmüller.[4]

The most frequent etiological factor is an inflammation of the ear, with or without mastoid, sinus or labyrinth involvement, and in these conditions the presence of this syndrome is of great importance both from the viewpoint of the diagnosis and also of therapy.

The following cases are cited as illustrations of different otitic pathological processes which may cause a reaction in the spinal fluid.

Case I illustrates the development of a meningitis sympathica in an individual showing otitis media without clinical signs of mastoiditis. The mastoid process was operated upon in this case with the hope of finding the focus which had given rise to the symptoms of meningitis:

Case I. Sam R., aged 10, admitted to the Otological Service of Dr. I. Friesner at Mt. Sinai Hospital May 4 and discharged May 26.

The patient complained of pain in the right ear, with discharge, for three days. This was preceded for two weeks by infection of the upper respiratory tract.

The physical examination on admission showed a rigid neck, bilateral Kernig and a positive Brudzinski.

FIG. 43. Temperature chart of a patient with otitis media.

May 4, before operation, 5 c.c. of a slightly turbid fluid, under increased pressure, were removed. There were 1100 cells per cubic millimeter, 85 pes cent polymorphonuclear leucocytes; no bacteria were found.

There was a slight amount of pus in the mastoid cells. An area of the dura, the size of a nickel, was exposed, and was found to be yellowish, gray and thickened.

May 7, the temperature fell, the Kernig sign and rigidity disappeared, and the child was discharged on May 26 as cured.

Case II illustrates the presence of an old otitis media, with no clinical signs of mastoiditis but a thrombosis of the lateral sinus, giving rise to symptoms of meningitis sympathica. The operation relieved all the meningeal symptoms. Subsequently a radical

mastoid was performed and a choleasteatoma removed. The patient has remained well since that day. This case is important in showing that the reaction of the spinal fluid can take place in the presence of a sinus thrombosis.

Case II. Sidney G., 11 years old. Admitted on April 7, 1924, with a diagnosis of left mastoiditis, with meningitis and septicemia as complications. Discharged April 28, 1924.

A year ago, following a cold, the ear was opened by a physician. The patient experienced no difficulty with the ear up to two months ago, when, because of acute otitis, the ear was incised and discharged freely. The discharge ceased up to two weeks ago, when fever developed and the ear was again incised. There was little drainage for two weeks, and then he began to complain of headache, although there was no pain in or behind the ear.

The physical examination showed eyes negative; moderate rigidity of neck and retraction of head; positive Brudzinski; suggestion of bilateral Kernig, no Babinski, Gordon or Oppenheim. Temperature, 104°F. The preliminary diagnosis: acute meningitis. Dr. I. Friesner stated that there were no signs of mastoiditis.

On the day of admission the blood count was: white blood cells, 21,000; polymorphonuclear neutrophils, 92 per cent; lymphocytes 8 per cent. Lumbar puncture on April 7 yielded 35 c.c. of a cloudy spinal fluid. Cytology: 2000 cells per cubic millimeter; albumin 4 mm. ring; globulin increased, and no tubercle bacilli or any other bacteria were seen in direct smears or cultures; 90 per cent polymorphonuclear cells, and 10 per cent lymphocytes.

April 8, 1924, the left mastoid was exposed, but no inflammation was found; the dura was then exposed, both in the middle and posterior fossa, but no pathological process was seen. The sinus was exposed and a thrombosis discovered. The sinus was ligated. The same day lumbar puncture yielded 40 c.c. of cloudy spinal fluid, 95 per cent polymorphonuclear cells, 5 per cent lymphocytes. Cytology: 13,440 cells per cubic millimeter; albumin 5 mm. ring; globulin increased. Wassermann negative. Direct smears showed many pus cells but no bacteria.

April 9, 1924, a negative report was received for the blood culture taken before the operation.

April 10, 1924, Dr. Baily reported that the pupils were normal, with no extraocular palsies. The visual fields were normal, and both discs were hyperemic, the details were blurred and the margins were obscured. The retinal veins were dilated and tortuous. Diagnosis: beginning optic neuritis.

April 12, 1924, white blood cells, 14,000, polymorphonuclear neutrophils, 82 per cent, lymphocytes, 18 per cent; cells counted, 100.

April 13, 1924, spinal puncture was performed and 20 c.c. of a clear fluid under moderately increased pressure were removed.

The boy was discharged improved. Subsequently he was readmitted to the hospital, a radical mastoid operation was done on the left ear and a cholesteatoma was removed. The patient was then discharged cured.

Case III illustrates the development of a meningitis sympathica in an individual who had been operated upon, not only for acute

mastoiditis and sinus thrombosis, but in whom infection of both lateral sinuses had persisted despite the operation, with the persistence of meningitis sympathica but without the development of an acute operative meningitis.

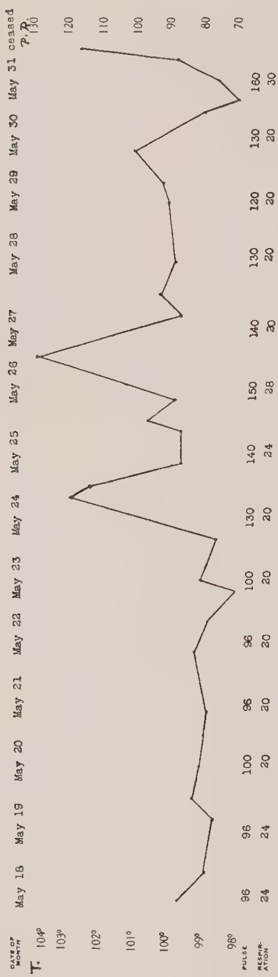

Fig. 44. Temperature chart of a patient with infection of both lateral sinuses.

Case III. William B., aged 21, was admitted to the Otological Service of Dr. I. Friesner at Mt. Sinai Hospital, May 18, 1922 and died June 3, 1922.

The patient had been suffering with headaches for seven months. He had been operated on for an acute mastoiditis at the Norwegian Hospital on November 10, 1921, and for sinus thrombosis on November 17, 1921. He recovered from both operations, but at intervals of a few days to a week he had attacks of pain in the head, with a temperature of from 103° to 105°F., accompanied by sweating and prostration. The spinal fluid on many occasions was clear. There was no increased pressure. The culture was sterile. There were 14 to 17 cells per cubic millimeter.

On admission, May 18, 1922, the examination showed a rigid neck, bilateral choked disc and a moderate bilateral Kernig. Under increased pressure, 10 c.c. of spinal fluid were removed and found to be clear; it contained 1 lymphocyte per cubic millimeter.

May 19, the exploration of the left mastoid and temporosphenoidal area proved negative.

May 24, 10 c.c. of clear spinal fluid, under slightly increased pressure, were removed. The fluid contained 350 cells per cubic millimeter, largely polymorphonuclear in character.

May 25, an exploration of the cerebellum proved negative.

June 1, 10 c.c. of clear spinal fluid were removed. The fluid was under slightly increased pressure and contained 150 cells, chiefly lymphocytic in character.

The patient grew steadily worse, running an irregular temperature. The pulse was rapid and of a poor quality. He was drowsy most of the time, and irrational. He died June 3.

The post mortem showed no evidence of meningitis. Both lateral sinuses at the tentorium were filled with pus. The sinuses communicated with one another.

Case IV illustrates the presence of a meningitis sympathica in an individual who has both mastoiditis and labyrinthitis. The marked meningeal reaction was unquestionably due to the labyrinthitis. In this type of case, unless operated upon, the patient almost invariably dies from an acute suppurative meningitis, self-imposed upon the meningitis sympathica. In many cases there very frequently develops from the acute labyrinthitis an acute suppurative meningitis before there is an opportunity for operation. The most favorable time for operation is when the acute process has subsided. There is even then a danger of an acute suppurative meningitis following the operative procedure, in subacute or chronic cases.

Case IV. Anna H., 26 years old, admitted to Otological Service of Dr. I. Friesner at Mt. Sinai Hospital, January 29, 1922; discharged April 24, 1922.

The patient complained of pain in the left ear for four days, and a discharge for one month. Two weeks ago there occurred attacks of vomiting, staggering and dizziness. The examination on the day of admission revealed a granuloma springing from Shrapnell's membrane. There was an occasional rotatory nystagmus on looking to the right, but no other neurological signs were found. Five c.c. of turbid spinal fluid, under increased pressure, were removed containing 4400 cells per cubic millimeter, 90 per cent polymorphonuclears.

January 30, total deafness of the left ear developed. There was no caloric reaction from the left labyrinth. There was a definitely rigid neck and bilateral Kernig. Fifteen c.c. of spinal fluid were removed under increased pressure, con-

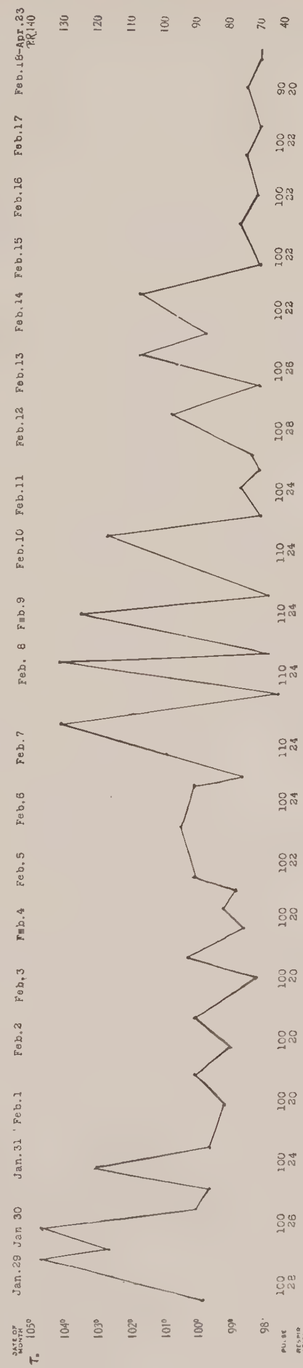

FIG. 45. Temperature chart of a patient with both mastoiditis and labyrinthitis.

taining 6400 cells per cubic millimeter, 90 per cent polymorphonuclears with no bacteria in the culture. The next day, January 31, the same quantity of fluid was removed, and 1060 cells per cubic millimeter were found, 90 per cent polymorphonuclear, with no bacteria in the culture.

February 4, there was a left facial paresis of the upper branch, and the fluid showed 1200 cells per cubic millimeter, containing many lymphocytes and no bacteria.

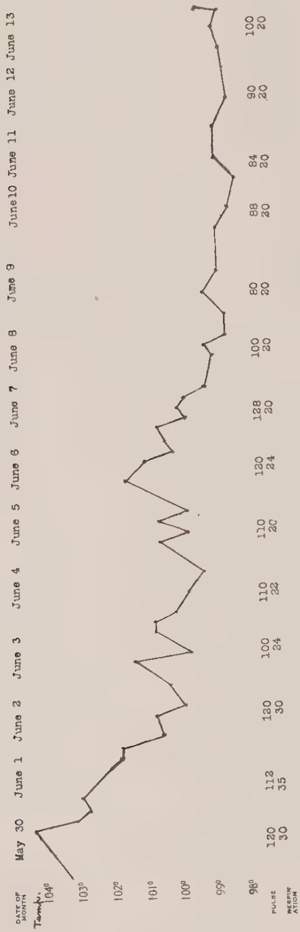

Fig. 46. Temperature chart of a patient with meningitis sympathica and complications.

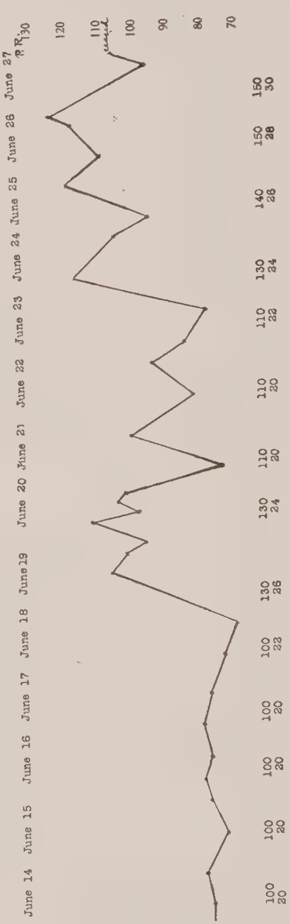

Fig. 46-A. Temperature chart of a patient with meningitis sympathica and complications. (*Continued.*)

February 13, a radical mastoid operation and labyrinthectomy were performed, and on the 17th the facial paresis was almost gone.

The patient was discharged on April 24 as cured.

Case v illustrates the development of a meningitis sympathica in an individual suffering not only from inflammation of the mastoid and a perisinuous abscess, but also having an epidural

and temporal lobe abscess. Despite operation, this patient developed an acute suppurative meningitis. The presence of the meningitis sympathica indicated to the surgeon the possibility of an intracranial complication, and prompted exploration of the cranial cavity.

Case v. Irving M., aged 10 years, was admitted to the Otological Service of Dr. I. Friesner at Mt. Sinai Hospital, May 31, 1923 and died June 29, 1923.

The patient had had a chronic ear condition for the past two years. For the three days preceding admission he had pain in the right ear. On the morning of admission he had a chill, felt drowsy, was stuporous, did not respond to questions and started vomiting. His neck was rigid; he had a bilateral Kernig and right Babinski; and his left pupil reacted more strongly than did the right. Spinal puncture yielded 10 c.c. of cloudy fluid, under increased pressure, containing 3500 cells per cubic millimeter, all polymorphonuclears and no bacteria. June 1, there were 4000 cells per cubic millimeter, mostly polymorphonuclears, no organisms. There was no caloric response from the right ear.

June 2, 5 c.c. of fluid were removed, under slightly elevated pressure, containing 4400 cells per cubic millimeter, mostly polymorphonuclears, with no bacteria present. June 4, 5 c.c. of clear fluid, containing 220 lymphocytes and no bacteria, were obtained.

He was operated upon on June 5 and a mastoiditis and perisinuous abscess were found. The pus in the mastoid was foul. There was an epidural abscess on the floor of the middle fossa, communicating with a large temporal lobe abscess. June 9, the neck was rigid but the Kernig was somewhat diminished. June 19, the neck rigidity and the Kernig were more marked, and the fluid showed 4000 lymphocytes, no bacteria. June 24, the fluid showed 1500 lymphocytes and was under increased pressure. Gram-positive cocci were present in both smear and culture.

June 28, the fluid showed 1200 lymphocytes, was under increased pressure, and Gram-positive cocci were present in both smear and culture. The patient died June 29.

Case vi is one in which the source of infection was undoubtedly from a chronic ear and mastoid inflammation. This had resulted in the development of an abscess, and the reaction of the spinal fluid indicated the presence of an intracranial complication demanding interference. Unquestionably, had the spinal fluid been examined earlier in the course of the disease, changes in this fluid would have been noted and earlier operative interference undertaken. The result of such an operation might have been favorable.

Case vi was admitted to the Otological Service on November 8 and died November 11, 1918.

Five weeks before admission, following removal of a polyp from the right ear, the patient developed a severe pain in the right side of the head, with a con-

tinuous temperature of 104°F. He appeared septic, and complained of dizziness on attempting to stand. The patient also vomited several times.

The physical examination showed a slight right facial paresis; marked nystagmus to the right; moderate nystagmus to the left; bradycardia, and marked adiadochokinesis. November 9, Dr. K. Schlivek reported that the optic nerve heads were red and the veins were slightly engorged, otherwise negative.

November 10, Dr. S. Oppenheimer performed an exploratory mastoidectomy, exploratory craniotomy and decompression. The mastoid showed an ivory-like hardness with a complete obliteration of mastoid cells. There was no exudation about the sinus. The dura mater of the temporal fossa was exposed but presented no exudation. The antrum of the ear was large and filled with pus. Decompression: the squamous portion of the temporal bone was denuded, and the dura mater was exposed over an area 1½ inches in diameter; intracranial pressure was markedly increased but the dura mater was clean, with no exudation. Lumbar puncture showed a clear spinal fluid, under moderately increased pressure, containing 300 cells, 80 per cent of which were mononuclears and the remainder polymorphonuclears. Smear and culture were negative: albumin, 4 mm.

November 11, Dr. Schlivek reported a slight bilateral papilledema, and on the same day Dr. Oppenheimer performed a craniotomy and drainage. The skull was opened over the cerebellum and the dura mater over the cerebellum was also opened. A grooved director located an abscess cavity in the cerebellum, and this was drained. A smear from the pus showed the presence of a Gram-positive coccus. Culture: Staphylococcus aureus. The patient died on the night of the second operation.

It very frequently happens in cases of acute otitis that, either while the acute process is still present or after it has subsided, and even after the perforation of the tympanum has healed, symptoms of meningitis develop. A lumbar puncture done at this time shows an increase in pressure of the cerebrospinal fluid and the presence of a large number of polymorphonuclear leucocytes. This fluid when examined both by culture and by smears appears to contain no bacteria. A number of days may elapse during which the symptoms of meningitis persist and are aggravated, and yet no bacteria are found in the spinal fluid after repeated examinations.

Finally, a day or two before exitus, which is the usual outcome of a case of this kind, bacterial growth is obtained. Cases such as these are not to be regarded as meningitis sympathica, but as instances in which, for some reason as yet unknown, bacteria cannot be demonstrated in the spinal fluid. It is possible that the organisms are present in the meninges, but not freely in the fluid, and that the few that do enter the fluid are disintegrated by bactericidal action. Possibly a period elapses before the organisms

become so abundant that the bactericidal power of the cells lining the subarachnoid space is unable to cope with the invasion, and the bacteria are then demonstrated. These cases must be regarded from the onset as cases of acute meningitis, and have not the significance of meningitis sympathica.

Meningitis sympathica occurs where there is a brain abscess. Whether or not such an abscess is associated with an inflammation of otitic or accessory sinus origin, it is always a symptom of grave portent. It is an indication that the inflammatory focus is not under control, and unless this focus is adequately attacked, acute meningitis is certain to develop; or in a case of brain abscess the patient will succumb to the inflammatory process. As an illustration of this may be cited a case which has already been reported by one of us (Strauss).[5]

Case VII. The patient was suffering from orbital cellulitis of nine days' duration. He was admitted to the service of Dr. Elsberg on November 29, 1913. The orbit was incised and drained. The next day lumbar puncture showed 15 c.c. of turbid spinal fluid under tension. The cells were increased and were all polymorphonuclear in character. The fluid contained only a contaminating Staphylococcus albus. This finding means that there was a meningitis sympathica and that the inflammatory process or a toxin had reached the meninges.

The patient was considerably improved by operation, and yet irritation of the meninges warned against a too hopeful prognosis. Thirteen days following the operation, although the patient was doing well, another lumbar puncture was done and 20 c.c. of slightly turbid fluid under a pressure of 160 mm. were obtained. The fluid contained 133 cells to the cubic millimeter, with a greater proportion of mononuclear than polymorphonuclear leucocytes. The albumin content was increased. The cultures were sterile. These findings were a positive indication that the patient was not out of danger.

The patient left the hospital apparently cured December 30, 1913.

March 10, 1914 (three months after discharge), he was readmitted because of severe headaches in the right temporal region. There was no evidence of accessory sinus disease. The eye examination was negative. Lumbar puncture disclosed a clear fluid under increased tension, but without an increase in the number of cells. The patient was discharged with the diagnosis of a periostitis of the frontal bone.

June 25 (three months after his second discharge), he was readmitted because of severe headaches in the same region as previously. Drowsiness and vomiting, and symptoms of increased intracranial pressure were present. After admission he had a convulsion. Lumbar puncture showed a fluid under increased pressure, with an increased albumin content, increase of polymorphonuclear leucocytes, and no bacteria. This was evidence of renewed meningeal irritation. Operation: frontal lobe exposed. It appeared soft and the pia over it was edematous, but no abscess was found.

August 20, the patient was discharged, improved.

He was subsequently admitted to another hospital, where repeated lumbar puncture yielded a sterile turbid spinal fluid. A diagnosis of brain abscess in the right frontal lobe was made and the lobe explored, but without result. Autopsy revealed an abscess in that lobe.

Another case of similar nature, also previously reported (Strauss),[5] is cited to show that meningitis sympathica may persist for a long time in the presence of a non-suppurative intracranial focus which has been operated upon. There is then evidence of the presence of another focus which has not as yet been localized. In the case cited this focus finally caused the development of acute suppurative meningitis and death. It was situated at the apex of the petrous portion of the temporal bone, a location which unfortunately cannot be reached by surgical means.

Case VIII. M. G. was admitted August 12, 1908. Four years ago the patient had pain in right ear for which the drum was incised. Following this incision the ear discharged pus for three months. Six weeks before admission the patient had a gangrenous appendicitis. Eight days before admission he had a profuse discharge from the right ear and two days later developed severe headache. Temperature, 102°F. The patient was prostrated and vomited several times. There were marked rigidity of the neck and a herpes labialis. There had been no chill and no pain over the mastoid.

Physical Examination. The mastoids showed no tenderness or swelling. The knee-jerks were exaggerated but there was no clonus or Babinski. The neck was rigid and the Kernig was marked. The symptoms pointed to a meningitis which did not appear to be of the ordinary cerebrospinal type, for which the ear was regarded as the probable cause. Lumbar puncture showed 25 c.c. of turbid fluid under markedly increased tension, polymorphonuclear leucocytes 80 per cent, with no bacteria. Aseptic polymorphonuclear meningitis was diagnosed and operation for brain abscess was advised.

August 13, operation by Dr. Wolff. The right mastoid cells were found to be practically sclerosed. The antrum was exposed and was found to be filled with a mass of cholesteatomatous material, as was also the middle ear. The sinus was normal. The dura mater was exposed and found pulsating. No epidural abscesses were found. It was not considered advisable to aspirate the brain at this time.

August 14, the pulse was 72 to 80; headache was present; there was less pain over the right ear. A right facial palsy was present. The cerebrospinal fluid showed 85 per cent polymorphonuclear leucocytes.

August 15, the patient was better and had much less headache and less rigidity of the neck; the Kernig was less marked.

August 19, there was some edema of the eyelids, especially the lower. The eye-grounds showed an edema and infiltration of both retinae, especially of the left eye. The retinal vessels were raised and the structure of the retina looked blurred.

August 22. The eyes were examined by Dr. Friedenberg. The pupils were dilated, the right disc was slightly hazy, the veins were tortuous, and the retina near the disc was slightly edematous. There was a slight pallor of the temporal half of the disc.

September 6, first dressing. A profuse discharge from the mastoid was present. Following operation the patient had a temperature of 99° to 102°F. He had a rigid neck and Kernig's sign.

September 7, there was a very profuse discharge, the wound being still open.

September 12, the packing was removed. The rigidity of the neck and the Kernig were not so marked.

September 20, lumbar puncture showed a cloudy fluid; polymorphonuclear leucocytes, 71 per cent.

September 22, the meningitis symptoms were still marked. Lumbar puncture disclosed 25 c.c. of turbid fluid; polymorphonuclear leucocytes, 85 per cent. After each puncture the patient's symptoms were temporarily relieved.

September 24, the symptoms were still present and the patient was worse. Temperature, 103°F.; pulse, 80.

Exploratory craniotomy by Dr. Oppenheimer to locate the focus. The dura mater was under marked tension. An area of dura mater about the size of a fifty-cent piece was exposed but no pus or purulent cerebrospinal fluid escaped. With a scalpel, punctures of the brain were made in four or five directions, but each time with a negative result. The dura was closed. The line of suture was closed by Cargile membrane and the wound packed with iodoform gauze.

September 25, following the operation the symptoms were more marked. The patient was delirious and lumbar puncture showed a fluid under tension and almost pure pus.

September 27, the condition was relieved after lumbar puncture and the patient was rational for a short time, and then died.

The first cerebrospinal fluids contained no bacteria; when the patient again became very sick, the fluid contained bacteria microscopically, but they would not grow. After the operation pure pus was found; it was considered probable that a brain abscess had ruptured.

Autopsy. At the apex of the petrous portion of the temporal bone there was an area of caries and necrosis. The pus was foul, thick and greenish and contained a variety of bacteria, most of which were Gram-positive bacilli. No abscess could be found anywhere in the brain, but the presence of practically pure pus in the vertebral canal shortly before death shows that an abscess which was probably present previously had ruptured into the ventricle. The patient evidently had three attacks of so-called "meningitis sympathica." These were probably due to an infection of the canal by anaerobic bacilli which did not multiply sufficiently to cause a progressive meningitis.

Case IX presented chronic inflammation of the middle ear and mastoid, with an acute exacerbation. On the second day after admission, there was evidence of a beginning irritative process of the meninges, shown by increased pressure of the spinal fluid and the presence of twenty lymphocytes per cubic millimeter.

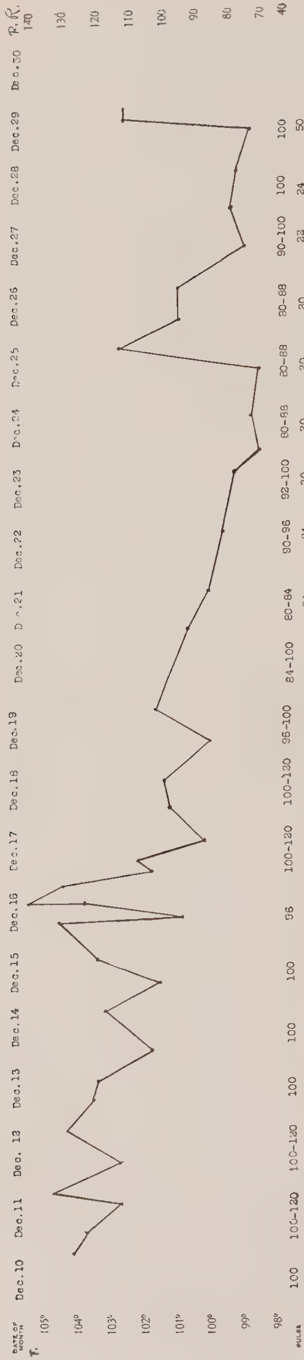

FIG. 47. Temperature chart of a patient with chronic inflammation of the middle ear and mastoid.

For five days thereafter no extension of this irritation was noted, then a lumbar puncture was performed, and a well-advanced meningitis sympathica was found to be present. The analysis of the case indicates that the inflammatory process attacked not only the mastoids but the sinuses and the perisinuous tissue, and then advanced intracranially, producing a large abscess in the cerebellum. During all this period the meningitis sympathica was indicative of an intracranial complication, and a number of days supervened before a bacterial meningitis made its appearance. It is interesting to note that the blood culture in this case showed a bacteriemia before the organisms could be demonstrated in the cerebrospinal fluid. The signs of cerebellar involvement in this case were extremely slight, and it is a question whether this abscess in the cerebellum had not existed for a number of days previous to the admission of the patient to the hospital and even before the meningitis sympathica was present. There is no method, however, of proving this point. The case could not be operated upon when the meningitis sympathica was discovered because of the presence of an erysipelas.

Case IX. Anna N., aged 51, was admitted to the Otological Service of Dr. I. Friesner on December 10, 1924 and died December 29, 1924.

The patient had been complaining of a left hemicrania for the past twelve days. For two years she had had a persistent foul discharge from her left ear, and for twelve days before admission the discharge had become very profuse. The left ear became red, tender and swollen the day before admission. The patient also stated that she had a distinct chill the day before admission. There was no vertigo, vomiting or tinnitus.

Physical examination revealed an acutely ill woman holding the left side of her head and complaining of very severe pain. There was a profuse, foul, purulent discharge from the left ear from a perforation in Shrapnell's membrane. The drum was thickened and no landmarks could be made out. The hearing was markedly diminished, and there was an exquisite tenderness over the mastoid and the emissary vein. Over an area of three inches in diameter, completely surrounding and including the left auricle, the skin was red, tender, swollen and sharply demarcated.

Provisional diagnosis: erysipelas, acute exacerbation of a chronic middle ear suppuration with intracranial involvement.

Blood count: white blood cells 19,400, polymorphonuclear leucocytes 92 per cent, lymphocytes 8 per cent.

A lumbar puncture was performed, and 25 c.c. of clear spinal fluid, under markedly increased pressure, were removed and found to contain 20 lymphocytes. Smear and culture were negative. The blood culture was also negative.

December 11, the erysipelas was spreading. It was deemed advisable not to operate through an erysipelatous area but to wait for a subsidence of the erysipelas.

December 14, the discharge from the left ear seemed decidedly less.

December 16, a blood culture showed a hemolytic streptococcus in the flasks. The patient became irrational, still complaining of headache, and for the first time there was rigidity of the neck. Thirty c.c. of clear spinal fluid, under markedly increased pressure, were removed and found to contain 1200 cells, 92 per cent polymorphonuclear leucocytes.

The fundi were negative.

December 17, 20 c.c. of cloudy spinal fluid, under markedly increased pressure, were removed, containing 1330 cells, 90 per cent polymorphonuclear leucocytes.

December 18, the erysipelas was fading. The headache was persistent. The rigidity of the neck was much less marked.

December 21, 7 c.c. of clear spinal fluid, under slightly increased pressure, were removed, containing 320 cells, 80 per cent lymphocytes. Simple mastoidectomy was performed. The mastoid was found to be sclerosed. The bone on the outer antral wall and floor of the antrum was softened by disease. There was a large perisinuous abscess, and an escape of pus occurred from between the sinus plate and the sinus, in the angle between the middle and posterior fossae. The dura mater over the floor of the middle fossae was normal.

December 26, 20 c.c. of cloudy spinal fluid under markedly increased pressure, were removed and found to contain 3700 cells, 77 per cent polymorphonuclear leucocytes. A sinus operation was performed. The lateral sinus from the bulb to the torcular was found to be filled with a purulent thrombus. The inner sinus wall was very thick and closely adherent to the cerebellar dura mater.

December 27, 20 c.c. of spinal fluid, under markedly increased pressure, were removed, containing 1700 cells, 40 per cent polymorphonuclear leucocytes, 60 per cent lymphocytes. The patient became very dull and apathetic and showed marked spasticity of all extremities. She then lapsed into coma. The spinal fluid of this day was found to contain a hemolytic streptococcus, which was not reported until after an exploration of the left cerebellum on December 28 was found to be negative.

December 29, the patient died.

The post mortem showed that the dura in the operative wound was somewhat adherent. The piarachnoid was injected and showed a small amount of purulent exudate along both sides of the superior longitudinal sinus. A similar exudate was found over both temporal lobes and the base of the brain. The left cerebellar lobe contained a huge abscess, 5 × 5 cm., filled with yellowish pus. The abscess was located in the dorsolateral portion of the lobe. A recent thrombus was found in the lateral sinus from the bulb to the torcular. The jugular bulbs were negative. Section of the lateral sinus showed a septic thrombus containing Gram-positive cocci.

Meningitis sympathica may also be present in patients in whom there is an inflammation of the accessory sinuses of the cranium or even of the structures adjacent to it.

Meningitis sympathica must be differentiated from tuberculous meningitis, from the so-called aseptic meningitis, which in the opinion of the authors is probably a meningitis caused by an unknown focus and therefore of the same significance as meningitis sympathica, and from the reaction of the spinal fluid in poliomyelitis and encephalitis. Except in cases of tuberculous meningitis the differentiation cannot be made from a study of the fluid itself, but must be made from the other clinical symptoms and the course of the disease.

Discussion

The following questions submitted to Dr. Strauss before the Commission, together with the answers to them, are here reported verbatim.

Dr. Dana: What name does Dr. Strauss give to that class of cases, of which we used to see a great many in Bellevue Hospital, in which the patient had all the symptoms of a meningitic condition, usually of alcoholic origin, and in which on post mortem there was found merely an edematous condition of the brain? We used to tap those cases, and Dr. Janeway and the older pathologists gave them originally the name of "wet brain." Perhaps the term is incorrect, but some name should be given to it. What does Dr. Strauss call those cases —symptomatic meningitis?

Dr. Strauss: Cases of that type, if there is an increase in the spinal fluid content—and there generally is—would come under the head of a serous meningitis because these cases as a rule show merely an increase in the amount of fluid without any, or very little, reaction of a cellular type. Serous meningitis

is a different thing from meningitis sympathica. The point that I make is that in the latter there is a cellular reaction, along with the increase of fluid, resulting from an acute suppurative condition elsewhere; for example, in the middle ear. These cases have been sometimes designated as serous meningitis, but they are not true cases of serous meningitis; they should be classified under the heading of meningitis sympathica.

Dr. Barker: Has Dr. Strauss any idea as to the mechanism concerned in the development of meningitis sympathica?

Dr. Strauss: I have ideas, Dr. Barker, but no proof.

Let us take a concrete example of a sinus thrombosis secondary to an otitis media and a mastoiditis. That sinus is exposed and there may be found a considerable degree of perisinusitis, even to the extent of pus in its neighborhood. However, that perisinusitis may be of such slight degree that macroscopically it is not noted. Probably in such a case there is also an inflammatory process on the inner surface of the dura mater; there may be a localized pachymeningitis, and from that localized pachymeningitic focus it is possible, in my opinion, that the irritative phenomena issue, which give rise to the cellular reaction in the spinal fluid.

Of course, there is another theory, if one uses as an example a case of an otitis media in which there is no mastoid inflammation clinically, and even when the surgeon operates he finds merely some hemorrhagic condition in the cells, very little softening, or occasionally a little focus of pus, and that otitis media may clear up; in fact, I have seen a case where the drum has healed, the patient was apparently doing well, and suddenly a slight headache occurred and a rise of temperature and symptoms of meningitis supervened. If you perform a puncture in such a case you find an increase in the polymorphonuclear leucocytes, some increased pressure of the spinal fluid, but neither in smear nor in culture are there any organisms. You may repeat that puncture day after day for a period of four or five days, the individual presenting all the symptoms of a meningitis and yet no organisms are obtainable. Finally, twenty-four hours before exitus, and sometimes a shorter period than that, you obtain the organism from the puncture either in smear or in culture, generally in both.

I have called attention to that type of case, for it might be looked upon as a meningitis sympathica, whereas probably from the very beginning it belonged to the infectious, inflammatory meningitides; but possibly because the organisms have not invaded the subarachnoid space in sufficient numbers to be obtained by culture or in sufficient numbers to avoid being destroyed by the protective mechanism within the subarachnoid space, we do not get those organisms in our culture until such time that they either flood it or the protective mechanism of the individual is unable longer to act as a barrier.

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Chapter XX

STUDIES OF THE CEREBROSPINAL FLUID IN INFANTS AND YOUNG CHILDREN*

STAFFORD MCLEAN, M.D., AND RUSTIN MCINTOSH, M.D.

Normal Infants and Children

FOR comparison with the data furnished by lumbar puncture in various diseases, the normal cerebrospinal fluid in children presents the following characteristics: clear and colorless, slightly alkaline in reaction, specific gravity approximating 1.002. Pressure is disregarded in the age group under consideration as it is greatly influenced by crying and muscular movements, and these cannot be controlled in infants. Globulin does not exist in demonstrable quantities in the normal cerebrospinal fluid of infants and when a definitely positive globulin reaction is present the fluid is considered pathological. Lymphocytes are normally the only cells present in cerebrospinal fluid; as many as twenty per cubic millimeter may be found in a normal child.

There is nearly always a positive reaction for a reducing substance, dextrose, which varies in amount as determined by the Folin and Wu method, between 45 and 85 mgms. per 100 c.c. of fluid.

The chlorides are so variable, 600 to 750 mgms. per 100 c.c. of fluid, that any constant relationship in their amount to any of the meningeal or extrameningeal infections has not been determined by us.

Cerebrospinal Meningitis

Thirty-five cases of cerebrospinal meningitis are presented, 23 of which were proved by the isolation of the meningococcus from the blood or cerebrospinal fluid and 12 by the clinical course and response to specific serum therapy, in addition to changes in the cerebrospinal fluid. Many of these patients were admitted in a

* From the Babies' Hospital.

moribund condition. Eleven were discharged as cured, 7 were improved and 17 died, of which 3 were autopsied.

These cases were from one month to four years of age; 13 were under six months of age and 25, or 69 per cent, were under one year of age. This is a striking commentary on the age incidence of the sporadic type of meningococcus infection. It seems probable that because of the mild character of the symptoms in many cases in infancy, a number of such infections remain unrecognized. In not a single instance was a clear fluid obtained by the first lumbar puncture, although in four instances the cell count was less than 500 per cubic millimeter. One specimen of fluid from which meningococci were obtained contained only 100 cells, yet was slightly turbid, due to the presence of fibrin. In most instances the fluid was described as turbid, but in two patients with counts over 10,000 it was frankly purulent in character. In a few cases the globulin test was not recorded. In all the others it was positive.

In 29 cases in which a qualitative test for sugar was made, it was negative in 24 cases, faintly defined in one, and in 4 cases definitely positive. Since the meningococcus possesses the power of fermenting glucose, it naturally follows that a diminution of the sugar content of the cerebrospinal fluid should be noted in the cases with moderately increased cell counts and a complete absence in the fluids with high cell counts, particularly those with purulent fluids. A quantitative estimation of the sugar in the cerebrospinal fluid from 16 patients was made. In the first or second lumbar puncture made after admission to the hospital, the fluid in 4 cases contained no sugar, 7 showed 26 mgms. or less per 100 c.c. of fluid and of the remaining 5 cases, 4 contained 45 mgms. and only one had a normal content of 65 mgms. per cubic centimeter, which was late in the disease when the cell count was only 110 and the culture showed no growth. These patients were admitted to the hospital during various stages of their infection. It is of interest to note the rise of the curve of sugar as the number of cells diminish with specific serum therapy.

Case 25121, four years of age. From the first lumbar puncture a cloudy fluid was withdrawn which contained 3000 cells per cubic millimeter and numerous meningococci. The fluid contained 20 mgms. of sugar per 100 c.c. Specific intraspinous and intravenous serum therapy was commenced immediately and during the period of hospitalization the sugar was determined quantitatively eight times. There was a gradual rise in the sugar content coincident with the decrease in the number of cells. At the eighth lumbar puncture the

cell count had diminished to 36 and the sugar had increased to 58 mgms. The patient was discharged cured.

Case 23558, E. A., eighteen months of age. The cerebrospinal fluid contained 4460 cells per cubic millimeter and 28 mgms. of sugar per 100 c.c. Meningococci were present in both the blood and cerebrospinal fluid. Ten cell counts were made during the period of treatment. At the next to last puncture only nine cells were present and the sugar had increased to 49 mgms. per 100 c.c. of fluid.

Of especial interest is case 24437, T. B., one month of age, who had two lumbar punctures and two cisternal punctures while under observation. In the first puncture 2620 cells were counted and the sugar content was 39 mgms. per 100 c.c. of fluid. No response to serum therapy was observed, and therefore only a slight diminution in the number of cells occurred. The sugar decreased before death to 18 mgms. per 100 c.c. of fluid and the count showed 1960 cells per cubic millimeter.

Encephalitis

Nine cases of encephalitis were studied, ranging in age from six months to five years, all but one of whom were discharged as improved. In only 5 cases was a pleocytosis present; the highest cell count on admission being 220 per cubic millimeter. In 5 of the cases a faint globulin reaction was present. The only constant finding of interest in these cases was a high sugar content which was noted in 4 out of 6 cases in which the estimation was made. In the other 2 cases the quantitative sugar was in the upper limit of normal. The 2 following cases are of especial interest on account of the chemical estimations.

No. 24771, T. S., eighteen months of age, admitted because of vomiting, drowsiness, rigidity of the neck and convulsions. At the initial puncture a clear fluid was withdrawn which showed 220 cells, 80 per cent of which were lymphocytes. The globulin test was negative and the test for a reducing substance was positive, 108 mgms. of sugar per 100 c.c. being present. Successive examinations showed 120, 150, 154 and 37 cells per cubic millimeter, and 108, 99, 62 and 27 mgms. of sugar per 100 c.c. of fluid, which demonstrates very nicely the decrease of the sugar with the disappearance of the evidence of meningeal irritation. The last sugar determination was much below normal and was obtained from a fluid showing only 37 cells. The patient was discharged cured.

Case No. 25485, B. T., three years of age, showed a persistently high sugar throughout the course of her disease which terminated fatally. She was admitted ou account of drowsiness, slurring speech, anorexia and convulsions. She was comatose on admission and remained so during the twelve-day period of observation. The first cerebrospinal fluid obtained was from a cisternal puncture. This showed 160 cells with a predominance of polymorphonuclears; a trace of globulin was noted and the test for a reducing substance was positive. The quantitative test for sugar gave 105 mgms. per 100 c.c. of fluid. Four other specimens of cerebrospinal fluid all obtained by lumbar puncture showed

only 108, 30, 1 and 2 cells respectively, yet the sugar remained constantly high, 89, 92 and 102 mgms. per 100 c.c. The temperature curve presented daily fluctuations between 101° and 105.6°F., once reaching 106°F. An autopsy, which was performed December 25, 1924, showed a rather friable brain with no gross inflammatory reaction in its coverings. (It is now in a hardening solution in preparation for further study.)

A predominance of the polymorphonuclear cells in the cerebrospinal fluid of this case may be explained by the fact that the first stage of encephalitis, like the first stage of poliomyelitis, is accompanied by a meningeal irritation which results in a polymorphonuclear cell increase. A marked leucocytic reaction of the blood in 6 of 7 cases with an average of 19,600 may be worth recording, but it would not serve as an aid in differential diagnosis since all infections of the central nervous system may at some stage be accompanied by a high white blood cell count.

ENCEPHALITIS DUE TO LEAD POISONING

The three following cases of encephalitis due to lead poisoning seem of sufficient interest to merit attention, especially since poisoning by lead is seldom considered as a diagnostic possibility in infants and young children. These cases will be reported elsewhere in detail by Dr. F. G. Beall.

R. G., four and one-half months of age, was nursed from birth, and thrived until three weeks before admission to the Babies' Hospital. Irritability was then noted, vomiting occurred frequently and eventually twitching of the right arm and the right side of the face was observed. On admission twitching of the right arm was observed in addition to a bulging fontanelle and exaggerated knee-jerks. Fever was not present. Routine examination of the blood disclosed marked basophilic stippling of the red cells, and on more complete investigation it was learned that the mother had used lead nipple shields for both breasts since her discharge from the maternity hospital. Lead was found in the mother's milk and in the stools of the infant. The first lumbar puncture showed a clear fluid with sixty cells, a trace of globulin and positive sugar reaction. The third lumbar puncture showed a turbid fluid; the first part withdrawn being slightly blood-tinged. It contained seventy cells, 80 per cent of which were polymorphonuclears. The reaction for globulin was marked. The quantitative sugar determination showed 46 mgms. per 100 c.c., the chlorides being 738 mgms. per 100 c.c. The third puncture showed a turbid fluid with 1130 cells, 93 per cent of which were polymorphonuclears. The reaction for globulin was marked. No lead was discovered in the spinal fluid. The infant was discharged cured.

H. L., a child sixteen months of age, died after a brief period of observation in the Babies' Hospital. Basophilic stippling of the red blood cells drew attention to the fact that lead poisoning was probably present. The infant's father was a painter; other than this no source could be discovered for the presence of the lead. The organs were removed at autopsy and lead was demonstrated. Only one lumbar puncture was done, which showed sixteen

cells and a positive globulin reaction. The qualitative reaction for sugar was negative.

S. K., No. 24663, a defective child twenty months of age, was admitted to the Hospital with the statement that for two months he had had a perverted appetite, had eaten paint off the furniture, bits of paper, etc. For two weeks vomiting had been noted, which just prior to admission became projectile in character. Drowsiness had been present for a day. This child succeeded in eating considerable amounts of freshly applied enamel from his bed during his early period of hospitalization. Basophilic stippling of the red blood cells was noted. On lumbar puncture a clear fluid was withdrawn which showed twenty-two cells, 74 per cent of which were polymorphonuclears. The globulin reaction was strongly positive. The quantitative sugar determination was 52 mgms., and the chlorides 713 mgms. per 100 c.c. of fluid. Four days later clear fluid was withdrawn by lumbar puncture which showed twenty-six cells, all of which were lymphocytes. The reaction for globulin was positive. A later puncture showed a clear fluid with fifteen cells, mostly lymphocytes. The globulin reaction was positive. The spinal fluid contained 72 mgms. of sugar per 100 c.c. and 675 mgms. of chlorides. The last lumbar puncture showed only four cells and 62 mgms. of sugar. Lead was found only in his stools. He was discharged improved.

Acute Poliomyelitis

Lumbar puncture was performed in 7 cases of poliomyelitis and polioencephalitis. The average age of these patients was nineteen and one-half months. Several of these cases were admitted to the hospital a number of days after the acute symptoms had subsided, which may account for the negative findings in the cerebrospinal fluid. All were discharged improved. In the 7 cases the fluid withdrawn was clear and colorless and in only 3 cases were more than twenty cells found. In 5 cases in which a test for globulin was done, it was positive in 4. The test for a reducing substance was positive in the 6 cases in which this examination was made.

Chemical analysis for sugar in 6 of the 7 cases showed the amount to be within normal limits in all. In 4 cases in which a quantitative determination of chlorides was made, all were within normal limits.

Case 23857, F.M., nineteen months of age. In this case five different chemical analyses for sugar and chlorides were made, and this case illustrates the variability shown in the chemistry of the cerebrospinal fluid in this condition. The patient was admitted because of the onset of vomiting, irritability and drowsiness and on admission and for several days thereafter the tentative diagnosis was tuberculous meningitis. Five lumbar punctures showed a clear fluid with 15, 5, 24, 14 and 4 cells respectively. The globulin test was positive in two out of four examinations. No organisms were obtained by smear or culture of the cerebrospinal fluid. The quantitative determination of sugar gave the following values per 100 c.c. of fluid: 71, 76, 62, 50 and 101 mgms.

Four were within normal limits with one in the lower zone of normalcy, while one was considerably above normal limits. This child was discharged improved.

From the evidence here presented in a small group of cases with chemical findings and confirmed by earlier observations of a large group of cases without chemical analyses, the only changes in the cerebrospinal fluid which will aid in the diagnosis in the acute stage of the disease is the cell count and a positive globulin reaction.

Tuberculous Meningitis

Nineteen cases of tuberculous meningitis are presented ranging in age from seven months to five and one-half years, with an average age of twenty months. In 16 cases the diagnosis was proved either by autopsy (in 9 cases) or by the discovery of tubercle bacilli in the spinal fluid. In 3 cases the diagnosis was made on the history, the course of the disease in conjunction with the result of the von Pirquet test and the cerebrospinal fluid findings. In 13 cases tubercle bacilli were found in the spinal fluid. This lower percentage of positive fluids than the general results at the Babies' Hospital may be explained by the short period of time that many of these cases were in the hospital, thus allowing of but one examination of the cerebrospinal fluid. No tubercle bacilli were found in the cerebrospinal fluid of case No. 25117. At autopsy only recent tubercles were present along the vessels and no fibrinous exudation, which explains the absence of organisms in the cerebrospinal fluid.

Although in several instances more than three hundred cells per cubic millimeter were counted, in every one of the 19 cases the fluid was clear and colorless.

There is an impression, which is a correct one, that lymphocytes are the predominating cell in the cerebrospinal fluid of tuberculous meningitis, especially in the early stages, and that polymorphonuclear leucocytes frequently predominate in the last stage. However, in 15 cases of this series, in the fluid from the first lumbar puncture, lymphocytes predominated in only 6, while in 7 the polymorphonuclears were in excess and in 2 cases the cells were equally divided. Many of the patients in this group were admitted in the later stages of the disease.

There is a wide variability in the number of cells. Several cases presented low cell counts, two contained less than fifty cells and the highest count in any of the 19 cases was 1260 cells.

The cellular reaction seems to bear no relationship to the number of tubercle bacilli in the cerebrospinal fluid. In one case with a cell count of but twenty, tubercle bacilli were discovered on the first examination, while in 2 cases proved by autopsy, each with more than three hundred cells, tubercle bacilli were not discovered in the cerebrospinal fluid.

In many cases repeated punctures in various stages of the disease fail to reveal a marked cellular reaction. Case 24662, proved at autopsy, showed 28, 84, 30 and 40 cells in four successive lumbar punctures. In 18 of the 19 cases in which a globulin examination was made, it was definitely positive in all, and in 13 the reaction was very marked. In 18 cases in which a qualitative test for a reducing substance was performed, it was positive in 8 cases, faintly positive in one and absent in 9 cases.

A quantitative estimation of dextrose was made in 13 cases, 12 of which were proved by autopsy or by the finding of tubercle bacilli in the spinal fluid. In only one of the cases was the sugar normal, in 12 it was definitely reduced, of which 3 showed the sugar content to increase toward the terminal stage. The highest dextrose content per 100 c.c. of cerebrospinal fluid was 75 mgms. Several specimens were examined which contained no sugar. The average for the cases in which a quantitative sugar determination was made was 28 mgms. per 100 c.c. It is thus apparent that there is a definite diminution of dextrose in tuberculous meningitis, which should at least serve as a help in the early differential diagnosis between this disease and encephalitis. It has been maintained by some that the chlorides are diminished, but in the 12 cases in which a quantitative determination of chloride was made the variability was so wide that there is little evidence of any diagnostic value in a chloride determination. Only extremely rarely at the Babies' Hospital has a case of tuberculous meningitis been autopsied in which general miliary tuberculosis was not demonstrated at the autopsy table. In eight of the nine autopsies in this series tuberculosis of the meninges was found to be only one phase of a general miliary tuberculosis.

Pneumococcus Meningitis

In 5 cases of pneumococcus meningitis, pneumococci were demonstrated in the cerebrospinal fluid. In 3 of the 5 cases organisms were also found in the blood stream. All of the 5 patients

died. The youngest patient was three months of age and the oldest was twenty-nine months. All the specimens of fluid, as would be expected, were turbid and the average count for the first lumbar puncture taken on admission to the hospital was 980 cells. In every case the globulin was strongly positive. The quantitative test for sugar was similar to the other purulent types of meningitis, being consistently low. The average for five examinations showed only 26 mgms. per 100 c.c. of fluid. The average chloride content for four examinations was 617 mgms.

Congenital Syphilis

Sixteen infants are listed under this diagnosis. They were from five weeks to twenty-seven months of age, six being under six months. In 7 cases the diagnosis was made on the blood Wassermann reaction alone. In the others, all of whom had positive blood Wassermann tests, it was made either at autopsy (in 5 cases), by florid cutaneous manifestations, or by a positive Wassermann in the cerebrospinal fluid. In 13 cases in which the globulin test was performed it was positive in 6, faintly positive in one and negative in 6 cases. The average cell count, excluding one case of syphilitic meningitis, was 30 per cubic millimeter. Five of the 15 cases had an increased number of cells. One infant with clinical syphilis and a four-plus blood Wassermann reaction gave a negative globulin test in the spinal fluid. Another clinical case with twenty-seven cells in the cerebrospinal fluid and a positive blood Wassermann reaction did not show any globulin reaction in the spinal fluid, but a third case, with a positive Wassermann reaction in the blood and in the spinal fluid, on three occasions gave a negative globulin reaction in one specimen of fluid and extremely faint reactions in two other specimens.

Of 11 patients, all with positive blood Wassermann tests, in whom the diagnosis was made by marked clinical manifestations, by a spinal fluid Wassermann test or by autopsy, only 5 showed an increased number of cells in the spinal fluid: 28, 160, 162, 27 and 504 cells per cubic millimeter respectively.

It was noted in a previous study of a larger group of cases, and again in this group, that congenital syphilis may involve the central nervous system without showing an increase in the number of cells in the cerebrospinal fluid.

The following case illustrates this point: No. 24732, R. C., aged eighteen months, was admitted because of drowsiness, muscular weakness and convulsions. The blood and cerebrospinal fluid gave a four-plus Wassermann reaction, and 66 mgms. of sugar per 100 c.c. of spinal fluid were found. Lumbar puncture on three different days showed one, two and two cells respectively, yet at autopsy a chronic leptomeningitis was found, in addition to visceral lesions associated with congenital syphilis. Nor does the severity of the cutaneous or visceral lesions bear any relation to the condition of the meninges as illustrated by case No. 24998, three months of age, which, in addition to a four-plus Wassermann reaction, had anasarca, nephritis and syphilitic epiphysitis, yet showed only four cells in the cerebrospinal fluid.

A reduction with Benedict's solution was a uniform finding in the cases of congenital syphilis.

In 9 cases in which a quantitative test for dextrose was made, it was within normal limits in 8 cases and definitely reduced in only one case. These findings would lead one to believe that the quantitative estimation of dextrose shows that it is present in normal amount in nearly every instance of central nervous system syphilis in infancy. In 9 cases in which a quantitative estimation of the chlorides was made, all were within the range of normal.

Of unusual interest is the following case of syphilitic meningitis (23945, R. G.) proved at autopsy:

R. G., a male infant seven and one-half months of age, was admitted to the Babies' Hospital on account of convulsions, weakness of voice, weakness of left arm, loss of weight and diminished excretion of urine. On lumbar puncture a faintly turbid cerebrospinal fluid was withdrawn which showed 504 cells per cubic millimeter, 80 per cent of which were lymphocytes. The globulin test was strongly positive, the qualitative reaction for sugar was negative. The quantitative sugar determination showed 20 mgms. per 100 c.c. of fluid and 700 mgms. of chlorides. One week later lumbar puncture showed 1580 cells, mostly lymphocytes, a positive globulin reaction and a faintly positive reaction for sugar. The quantitative sugar estimation showed 28 mgms. and the chlorides 688 mgms. A third puncture showed a diminished number of cells and an increase in the quantity of sugar, 37 mgms. per 100 c.c. of fluid and 610 cells per cubic millimeter. The blood and cerebrospinal fluid showed a four-plus Wassermann reaction. The mother's blood Wassermann test was also strongly positive. In a precipitate of the cerebrospinal fluid no spirochetes were found. The eye-grounds showed a low grade retinitis. The infant was treated vigorously with neosalvarsan intramuscularly and intravenously. He was also given salvarsanized serum intrathecally. Death occurred after six weeks of observation.

An autopsy revealed cerebral hemorrhagic pachymeningitis and cerebral and spinal syphilitic leptomeningitis, in addition to the usual visceral lesions of congenital syphilis.

CONCLUSIONS IN REGARD TO THE CEREBROSPINAL FLUID IN CONGENITAL SYPHILIS

1. The intensity of the cutaneous manifestations of congenital syphilis is not a criterion of the findings in the cerebrospinal fluid.

2. Congenital syphilis may involve the central nervous system as proved by a positive Wasssermann reaction in the cerebrospinal fluid without causing a cellular reaction in the fluid.

3. A quantitative chemical analysis of the cerebrospinal fluid for sugar and chlorides is not in itself a helpful diagnostic item in the diagnosis of neurosyphilis, but taken in conjunction with the other findings it may add another positive point.

4. In syphilitic meningitis there is a reduction in the amount of sugar present in the cerebrospinal fluid comparable to the reduction noted in other types of meningitis with high cell counts.

Bronchopneumonia

The cerebrospinal fluid of 20 infants was examined, in which the primary diagnosis was pneumonia. The majority of these cases were bronchopneumonia, many with complicating infections. The youngest case was twenty-eight days of age and the oldest was five years. Lumbar punctures were performed in these cases because of symptoms which suggested the possibility of a central nervous lesion. Of the 20 cases, 9 died.

In every case the fluid obtained was clear and colorless; in 4 cases the test for globulin was positive, in 2 instances it was questionable and in 12 cases it was negative. The qualitative test for a reducing substance was positive in all the cases. In specimens of the cerebrospinal fluid from several patients no cells could be found. The highest cell counts were ten, twelve, ten and eleven respectively, the average count for the 20 cases being four cells. The 4 cases with the highest cell counts died of pneumonia, the condition for which they were admitted to the hospital.

A quantitative sugar determination was made in 13 of the cases and in all it was within the range of normal, i.e., between 45 and 85 mgms. per 100 c.c. The average for the 13 cases was 67 mgms. per 100 c.c., which might be taken as a normal for infants and young children. The lowest amount found was 47 and the highest was 83 mgms. per 100 c.c.

A qualitative determination of chlorides was made in 13 cases. These varied between 638 and 738 mgms. per 100 c.c., which is within the normal range, i.e., 600 and 750 mgms. per 100 c.c.

Of interest is the fact that in these 20 cases, all of which had either one or more of such symptoms as irritability, rigidity of neck, vomiting, drowsiness, coma or convulsions, which led to the suspicion that the central nervous system might be invaded, not one had a very marked increase in the number of cells nor had any of the group a marked change in the amount of dextrose. The only finding which could be termed pathological was a positive globulin reaction in 4 of 20 cases, which in our opinion was possibly due to the presence of a few red blood cells incident to the trauma produced by puncture. This is a commentary both as to the frequency of such symptoms in pneumococcic infections and the unreliability of the clinical signs of central nervous involvement in this type of infection.

Disturbances of the Digestive System

In this group of 10 cases are placed such conditions as dysentery, acute intestinal indigestion and intoxication. The youngest patient was four months of age and the oldest eight years. The average age was 23.3 months. In every instance the fluid was clear and colorless. In 8 cases in which a test for globulin was made, it was positive in 3 cases and negative in 5 cases. The qualitative test for sugar was positive in all the cases. In 2 of the cases no cells could be found in the cerebrospinal fluid and only one case in which fifteen cells were found showed any appreciable cellular reaction.

A quantitative sugar determination was made one or more times in 8 of the cases. On the whole, this group showed a higher per cent of dextrose than the pneumonia group. The lowest showed 53 mgms. per 100 c.c. and the highest 140 mgms. per 100 c.c. The average for nine estimations was 97 mgms. per 100 c.c. as compared with 67 mgms. for the first-named group.

Several factors may have operated to cause this increase in sugar. Diarrheal cases admitted to an infant's hospital usually show a marked degree of dehydration as a result of frequent watery stools. In consequence, all of the body fluids including the cerebrospinal fluid would show varying degrees of concentration sufficient in many cases to increase the percentage of dextrose. In other cases, treatment for dehydration with frequent injec-

tions of fluid under the skin, intraperitoneally, etc., might for a brief interval induce a saturation of the body tissues with fluid, and in consequence a relative diminution of the solids, such as sugar, might occur. Many of these dehydrated infants are treated with hypodermoclyses of dextrose solution varying in concentration from 3 to 6 per cent. The introduction into the body of 15 to 30 gms. of dextrose in the course of a few hours has been shown to raise the sugar value in the cerebrospinal fluid.

The chief interest from a clinical standpoint is the high percentage of sugar in some of the cases in this group, especially among those in which drowsiness or stupor occurred.

Of interest is case No. 23532, E. M., who, during two attacks of diarrhea at intervals of a year, presented symptoms which pointed to an involvement of the central nervous system. The patient was admitted at the age of fourteen months because of vomiting and convulsions. Lumbar puncture revealed a clear fluid with fifteen cells per cubic millimeter, all of which were lymphocytes. The test for a reducing substance was positive. She was discharged cured, with the diagnosis of acute intestinal intoxication. She was readmitted at twenty-six months of age because of vomiting, drowsiness and convulsions. Lumbar puncture revealed only four cells per cubic millimeter, with a positive reaction for a reducing substance. The quantitative test for sugar showed 78 mgms. per 100 c.c. and 700 mgms. of chlorides. The blood Wassermann was negative. She was discharged cured with the same diagnosis as on the previous admission. This is a striking commentary on the tendency shown by certain children to manifest symptoms pointing to disturbance of the central nervous system in the presence of fever whether due to infection or to chemical disturbance. In infancy the most common nervous symptoms are vomiting, irregular respiration, exaggeration of the reflexes, irritability, drowsiness, stupor and convulsions. In childhood the commoner symptoms are restlessness as manifested by picking at the bedclothes, tossing about in bed, delirium, muscular tremor and coma. Some inherent defect in nervous tissue may possibly explain why certain children are prone to such symptoms in the presence of fever, while others escape them altogether.

Status Lymphaticus

Three cases of status lymphaticus were demonstrated at autopsy in which lumbar punctures had been performed during life. The ages were twenty-two months, sixteen months and five weeks respectively. In all 3 cases the spinal fluid was clear and colorless. The cell count showed four, six and twenty-five cells per cubic millimeter respectively on the first lumbar puncture after admission to the hospital. The reaction for a reducing substance was positive in all and the globulin test was positive in 2. The quantitative sugar determination was well below the normal limits in

2 of the cases and normal in one case. The chlorides were normal in all 3 cases.

Case No. 24242, P. F., is worthy of comment, having been admitted to the Hospital at the age of five weeks because of irritability, rigidity of the neck and drowsiness. The diagnosis during life was sepsis. At the first lumbar puncture a clear fluid was withdrawn which showed twenty-five cells per cubic millimeter, 60 per cent of which were polymorphonuclears. The test for a reducing substance was positive and the test for globulin which was made on the fluid removed at the first puncture was negative. Chemical analysis gave 33 mgms. of sugar per 100 c.c. of fluid and 725 mgms. of chlorides. A subsequent lumbar puncture showed a turbid fluid with 70 cells per cubic millimeter, 71 mgms. of sugar and 675 mgms. of chlorides. A culture of the blood showed no growth. At autopsy a hyperplastic thymus weighing 30 gms. and an acute splenic tumor weighing 23 gms. were noted in addition to an hypertrophy of the pituitary. It seemed likely that the infant's death had been hastened by the lymphatic state.

Cerebral Hemorrhage Occurring at Birth

The diagnosis of cerebal or cord hemorrhage can be made but rarely on lumbar puncture alone. Trauma produced by the needle frequently releases blood into the intravertebral canal. This is of such common occurrence in early infancy even when performed with the greatest skill that the diagnosis of cerebral hemorrhage cannot be made on the presence of a few red blood cells or a large amount of blood in the cerebrospinal fluid obtained by lumbar puncture. If, however, bloody fluid is obtained at the first lumbar puncture performed in the first few days of life and successive punctures show a gradual diminution in the amount of blood and eventually a clear fluid is obtained, it may be held that cerebral hemorrhage has occurred.

If a xanthochromic fluid is obtained by lumbar puncture in early infancy and the color does not disappear on standing or after centrifuging, it may be accepted as diagnostic of cerebral birth hemorrhage, on the natural assumption that the xanthochromia is the result of hemolysis.

The blood in the cerebrospinal fluid, caused by cerebral hemorrhage at birth, tends to disappear rapidly, and unless the hemorrhage has continued, it will disappear entirely, usually by the end of the second week of life.

Such manifestations of cerebral hemorrhage as drowsiness, feeble respiration, feeble cry, refusal to nurse and a gray color of the skin, with or without convulsions or a bulging fontanelle, are

of greater significance to the clinician than the presence of a few red blood cells which may have resulted from trauma.

In the following group of cases lumbar puncture was made to exclude the possibility that an infection of the central nervous system might have caused such symptoms as irritability, rigidity of the neck, exaggerated reflexes, convulsions, etc. Many of the infants were too old for the examination of cerebrospinal fluid to be considered as an aid in the diagnosis of cerebral hemorrhage due to birth trauma. The diagnosis on discharge was made on the history of a difficult labor, the condition of the infant during the first few days of life plus the usual residual physical findings, supposedly denoting birth hemorrhage.

Of the 15 cases from two days to twenty-two months of age with an average age of six months, only 3 showed a xanthochromic fluid. These were two days, five days and two months of age respectively. The average cell count for 15 cases was 5.4 cells per cubic millimeter. One of the xanthochromic fluids showed 14 cells and another 20 cells per cubic millimeter. None of the specimens of cerebrospinal fluid showed an increased cell count. The globulin reaction was positive in 4 of 14 cases, and the test for a reducing substance was positive in the 10 cases in which the examination was made.

A quantitative test for sugar was performed sixteen times in 11 patients, all being practically within normal limits. An infant two days of age with xanthochromic fluid showed only 44 mgms. of dextrose per 100 c.c., which was confirmed on subsequent examination. A quantitative determination of chlorides was made on 11 patients with sixteen examinations, all being within the range of normal.

Conclusions

1. In cerebrospinal meningitis the sugar content of the cerebrospinal fluid is diminished in cases with moderately increased cell counts and absent in the fluids with high cell counts, particularly purulent fluids. A gradual increase in the sugar was noted coincident with a decrease in the number of cells.

2. In a small group of cases of encephalitis the only uniform finding of diagnostic interest was a sugar content higher than in any other type of case.

3. In 3 cases of encephalitis due to poisoning by lead the test for globulin was positive and in 2 of 3 cases there was a pleocytosis.

4. In tuberculous meningitis the cellular reaction seems to bear no relationship to the number of tubercle bacilli in the cerebrospinal fluid.

5. A diminution of dextrose was noted in the cerebrospinal fluid of tuberculous meningitis, which might serve as an aid in the early differential diagnoses between this disease and encephalitis.

6. There is little evidence, of any diagnostic value, in a chloride determination in tuberculous meningitis or in any other meningeal or extrameningeal condition in infancy and early childhood.

7. In a small group of cases of pneumococcus meningitis the dextrose content of the cerebrospinal fluid was similar to the other purulent types of meningitis; that is, consistently low.

8. It was noted in a previous study of a group of cases of congenital syphilis and again in this group that congenital syphilis may involve the central nervous system without showing an increase in the number of cells in the cerebrospinal fluid.

9. The quantitative estimation of dextrose in the cerebrospinal fluid of congenital syphilis showed it to be present in normal amounts in nearly every instance. In syphilitic meningitis there is a reduction in the amount of dextrose present in the cerebrospinal fluid comparable to the reduction noted in other types of meningitis with high cell counts.

10. In 13 cases of pneumonia the dextrose content of the cerebrospinal fluid was within the range accepted by us as normal. The highest cell counts in 20 cases were ten, twelve, ten and eleven respectively.

11. In a group of cases of disturbance of the digestive system an increased amount of dextrose was found, perhaps because of the concentration of body fluids due to diarrhea and the introduction into the body of dextrose solution as a therapeutic measure.

12. If a xanthochromic fluid is obtained by lumbar puncture in the first few weeks of life and the color does not disappear on standing or after centrifuging, it may be accepted as evidence of cerebral hemorrhage. The presence of red blood cells in the cerebrospinal fluid obtained by lumbar puncture in the first few weeks of life is not diagnostic of cerebral hemorrhage, since the factor of blood introduced by trauma at the time of puncture cannot be excluded.

* * *

The following remarks were made by Dr. McIntosh in explanation of a graphic presentation of the chemical results obtained by the authors of this paper:

Dr. McLean has given you our clinical figures. In the course of eighteen months, we investigated the chemistry of approximately 500 fluids. Our greatest difficulty lay in determining the normal values, and while he gave our normal figures as from 45 to 85 mgms. of sugar and from 600 to 750 mgms. of chloride per 100 c.c., there are great variations, particularly in infants who are under eighteen months of age. Only a few cases fall into definite groups where the chemistry of the cerebrospinal fluids corroborates the clinical classification.

Figure 48 indicates a few curves of spinal fluid sugar values in cases of tuberculous meningitis. All of these were proved cases. These curves are plotted back from the date of death. If the zone, from 45 to 85 mgms., represents the normal level, it is obvious that the majority of the curves fall below the normal or in the low normal range. A descending slope of the curve during the progress

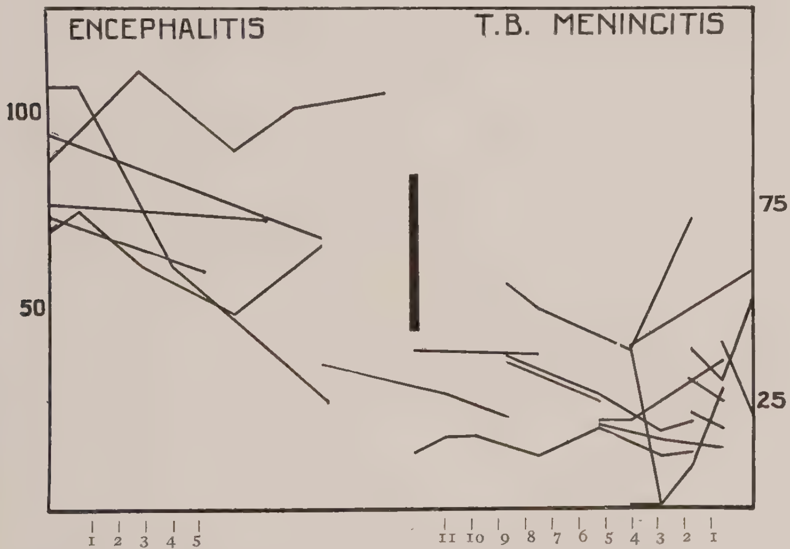

FIG. 48. Chart of curves of cerebrospinal fluid sugar values, in milligrams per 100 c.c., in cases of encephalitis and of tuberculous meningitis. (The short vertical lines beneath the chart represent intervals of twenty-four hours.)

of the disease is present in most of the cases, but not in all of them. In about 50 per cent there is a terminal rise in the last two or three days, which has been attributed to a concentration of the body fluids due to an inability to take fluids by mouth or to absorb fluids otherwise administered. There are a number of other single determinations which have not been put on the chart, but which corroborate these findings.

On the left appear 4 cases of encephalitis. These curves are plotted forward, beginning with the first observation, irrespective of the stage of the disease. Difficulty is immediately encountered in the classification of these cases. Are these all alike? Are they primary or are they secondary? Some of them were believed to be secondary. One interesting curve represents a case diagnosed as encephalitis following whooping-cough. The patient was eighteen months

of age and was admitted with symptoms of central nervous system involvement. The first spinal fluid sugar showed a level of 108 mgms.; the next one on the following day showed 108 mgms.; three days later it dropped to 62 mgms., and four days after that to 27 mgms. Why the values fell so far below normal was impossible to determine. The other cases were cases of encephalitis which were believed to be primary, so-called epidemic encephalitis. These were all in small infants and children in whom the diagnosis presented difficulties.

In meningitis due to pyogenic organisms nothing was found strikingly different from the results found in adults, except that the general trend of the sugar level is lower than in adults. The normal values that Schloss and Schroeder quoted, of 50 to 135 mgms. per 100 c.c., were higher than those encountered in this group. There was a difference in age grouping in those cases, which may have explained it.

In infections not involving the central nervous system, essentially normal values were found and in about 100 cases of this type, representing pneumonias and various other infections.

An interesting but baffling group is afforded by the cases of marasmus, feeding cases and those of acute intestinal intoxication which are frequently admitted with central nervous system symptoms such as convulsions, retraction of the head, hyperirritability, or stiffness of the neck, calling for a diagnostic lumbar puncture. A normal cell count has been invariably found, with no evidence of globulin in the ammonium sulphate ring test, but a great variation in the values of sugar has been found. The lowest was 26 mgms. per 100 c.c. and the highest was 156 mgms. In other words, in this type of case the normal level is indefinite. The reason for this is, I believe, the fact that these particular cases present varying degrees of dehydration.

A certain number of blood analyses of sugar and chlorides were made simultaneously with the spinal fluid examinations, which, however, showed no definite correlation.

The chlorides have been very disappointing, as they show variations, particularly in tuberculous meningitis, where there is a sharp fall in the level. From the point of view of a clinician, the chlorides are of very little help because, when the level of the chloride concentration has fallen, other diagnostic points are so numerous and the conditions so obvious that they are not of much help, nor do they aid particularly in prognosis. The cell count and the spinal fluid sugar have been of more aid to us.

Discussion

The following questions submitted to Dr. McLean before the commission, together with the answers to them, are here reported verbatim.

Dr. Spiller: Dr. McLean stated that the number of cells in the normal cerebrospinal fluid of young children is occasionally much higher than that which occurs in adults; twenty lymphocytes, he said, may be normally found. I should like to ask him whether he has any data which would justify the

assumption that repeated lumbar puncture would increase the number of those cells in cases where there were no distinct evidences of inflammation. Can irritation be produced by repeated lumbar puncture, increasing the normal number of twenty lymphocytes to forty, or more, suggesting a possible meningitis?

Dr. McLean: It has never been observed by us that repeated lumbar puncture increases the number of cells in the cerebrospinal fluid of normal infants and children.

Most of the lumbar punctures on infants and children found to be normal were naturally not repeated.

Dr. Spiller: I should like to ask a question which I do not see touched upon in this program, and yet I think that it is of very great importance. Does Dr. McLean think lumbar puncture has any influence on the spread of inflammatory conditions such as poliomyelitis and encephalitis? Does he recommend lumbar puncture in these diseases?

Dr. McLean: I am unable to answer the question. We do repeated lumbar punctures in infants and we have never seen any bad results. Dr. W. W. Herrick, in a paper in 1919, demonstrated that, in all varieties of medical conditions, lumbar puncture was not a harmful procedure. His experience included 5000 lumbar punctures.

Dr. Spiller: There is one other question. Dr. McLean spoke of lead nipple shields producing lead palsy in children. A few years ago I had that question brought before me very strongly. I went with it to Dr. John Marshall, who was then Professor of Chemistry in the Medical School at the University of Pennsylvania and asked him whether such a thing would be possible, and he told me that it depended very largely on whether the mother used mineral grease or vegetable grease on her breasts. If she used vegetable grease, it might produce a fatty acid which would readily combine with the lead in the shield and in that way produce lead palsy in the sucking child.

You spoke of that in your paper as a side issue, but have you had sufficient cases upon which might be based your opinion that a child could get lead palsy from a mother's breast when she has been using lead shields?

Dr. McLean: That is the only case we have had. Another case was reported from the Babies' Hospital two years ago, in which a mother who had had an eczema of her breast used an ointment which contained lead acetate. She wiped it off before the child was put to the breast, but this child developed a lead encephalitis. This lead nipple shield case is the only one of the kind which has come to our attention.

Dr. McKendree: Upon what basis has it been determined that normal infants may have as many as twenty lymphocytes in the spinal fluid?

Dr. McLean: The only proof offered is that we do a great many lumbar punctures in infants and young children. As many as twenty cells are not infrequently found in the cerebrospinal fluid in patients who have no discernible lesion of the central nervous system.

Chapter XXI

THE HUMAN CEREBROSPINAL FLUID IN THE ACUTE NEURAL AND EXTRANEURAL INFECTIOUS DISEASES*

JOSEPH C. REGAN, M.D.

THIS paper comprises distinctly three parts. The first portion is an attempted classification of the various meningeal syndromes occurring in connection with the infectious diseases, with the differential description of the spinal fluid in these conditions. The second portion represents the construction of the individual formulae showing the characteristics of the spinal fluid in the important acute neural and extraneural infectious diseases. The third portion is a tabulation of the spinal fluids not already covered in the preceding groups.

It seems advisable, by way of introduction to this group of acute neural and extraneural infectious diseases, to attempt first to classify and then to discuss briefly the type of meningeal reactions which the infectious diseases induce by their action on the central nervous system.

The everyday frequency with which meningeal syndromes are encountered in acute infections is common knowledge to all. Yet when an attempt is made to classify the type of reaction

* The major portion of the material used in the tabulations included in this article was obtained from the records of the Meningitis Division of the Research Laboratory, of which Dr. Josephine B. Neal is Director, and from the files of the Kingston Avenue Hospital Laboratory. The remaining portion was obtained through the courtesy of the staffs of the following hospitals, to whom ackowledgement is due: Bellevue, Presbyterian, Montefiore, St. Luke's, Lenox Hill, Mt. Sinai, Brooklyn, St. Mary's, Methodist Episcopal, and Brooklyn Jewish.

The collection of the data was carried out under the able direction of Dr. Josephine B. Neal with the cooperation of Dr. Henry W. Jackson, and Dr. Emmanuel Appelbaum.

The assistance of Dr. Neal rendered it possible to present the tabulated summaries of the findings in the cerebrospinal fluids in the various diseases included.

observed in the individual patient, it is at once seen that there is much divergence of opinion. A conflict of ideas exists, for example, in the use of the terms "meningism" and "serous meningitis." Some authorities would discard entirely the former and classify all such syndromes under the heading of "serous meningitis." On the other hand, many times there is no very distinct difference drawn by many writers between these two terms, and they are often used interchangeably. The majority of the cases termed "meningitis sympathica" have until recently been called "serous meningitis," the distinction not being clearly defined; this also applies to the term "aseptic meningitis."

In a separate group intermediate in position between the amicrobic meningitis syndrome and the true acute bacterial meningitis should be placed attenuated meningitis and localized meningitis.

A tentative plan of classification of these conditions seems to the writer, in a way, essential, not that it can be complete, but, since it will show the lack of knowledge of many fundamental considerations, it may excite frank discussion and criticism and in this way lead to more careful clinical and pathological studies of this group of meningeal conditions, which have been too much neglected considering the fact that their existence has been well recognized for more than a quarter of a century.

From the standpoint of the chemistry, cytology and bacteriology of the spinal fluid, corroborated by the pathological data which are available, it would seem to the writer that the meningeal syndromes encountered in the course of the acute infectious diseases may be divided into four classes:

I. Various forms of amicrobic meningitis
II. Various modified types of bacterial meningitis
III. Acute bacterial meningitis
IV. Various forms of acute meningoencephalitis

I. Various Forms of Amicrobic Meningitis

A. Meningism. This term, introduced by Dupré,[1] must still be preserved in the nomenclature of these conditions. It describes a class of meningeal reactions which occur especially in infants and children and which cannot be placed under any other heading. The symptoms are usually those of increased cerebrospinal fluid pressure which while varying in intensity, are often apparently grave. In reality they are benign, and from the

rapidity with which complete recovery occurs, they have evidently no such distinct underlying pathological basis as would justify their being placed with serous meningitis. Meningism, whether or not its origin be functional, may originate from a diverse variety of toxic causes in which the majority of the infectious diseases and many of the non-bacterial intoxications may at times be incriminated.

The spinal fluid in this condition is normal in appearance, in chemistry and in cytology. It may be divided into a form with normal tension and a form with hypertension.

B. Serous Meningitis. This term has so often been used synonomously with hydrocephalus that confusion exists as to the proper classification of the condition. It is differentiated from hydrocephalus by the fact that it is characterized by an acute course, that it is non-obstructive and that it is usually infectious and may be of inflammatory origin. However, it must not be forgotten that certain cases of serous meningitis exist which are of mechanical, chemical and rarely thermal origin.

A distinct pathological basis usually exists in this disease, the pathological change, however, varying greatly in its intensity and influencing the symptomatology and the spinal fluid findings. It must be distinguished from meningism, since in the latter there is evidently no decided pathological alteration in the meninges and no change in the normal cerebrospinal fluid findings. The causative factor is typically a toxemia, of infectious origin, which induces a change in either, or both, the secretion and absorption of the spinal fluid through disturbances of the chorioid plexuses, the ependyma or the meninges, resulting in an increase in the amount of the cerebrospinal fluid in the ventricles and subarachnoid space and a variable degree of edema of the brain. The symptoms are those of an increased cerebrospinal fluid pressure, generally responding well to treatment by means of lumbar puncture. Improvement, however, is proportionately dependent on the degree of severity which the edema of the brain tissue has attained. This acute serous meningitis may originate in any of the infectious diseases and in many of the toxemias.

Of the acute infections, which will be discussed later in detail, one may mention measles, scarlet fever, pertussis, influenza, pneumonia, epidemic parotitis, typhoid, typhus and erysipelas as those in which serous meningitis is most common. Of the more chronic diseases, tuberculosis and syphilis may be cited. Serous

meningitis may also be observed in acute infectious diseases of the central nervous system; for example, in the course of acute poliomyelitis and in epidemic encephalitis.

A local focus near or within the cranium or at a more distant site may also excite such a meningeal reaction; for example, an otitis media, mastoiditis, brain abscess, sinus thrombosis (Kopetzky[2]) sinusitis, septic sore throat, retropharyngeal abscess, bronchitis, pleurisy, peritonitis, enterocolitis, etc.

Certain non-bacterial toxemias may give rise to a serous meningitis, and while they may be placed in a separate sub-grouping they cannot be excluded from this heading. Among these toxemias one may mention alcohol, uremia, lead poisoning, food ("alimentary") intoxication, etc.

The types of serous meningitis may be grouped as follows:

1. The usual acute form
2. The "meningeal state" form (Widal)
3. The "meningitis sympathica" form
4. The aseptic meningitis form.

1. The usual acute form is characterized by a clear cerebrospinal fluid, under moderate to marked tension, showing pathologically only an increase in albumin and globulin content, or the presence of some pathological constituent such as alcohol, urea, acetone (in excess). This is the most frequent form.

2. The "meningeal state" form is limited almost entirely to the acute infectious diseases and is characterized by a further stage of inflammation and a cellular reaction of a variable degree. According to the evidence provided by the cerebrospinal fluid, it may be subdivided as follows:

a. Cases with a predominant lymphocytic formula (common)
b. Cases with a predominant polynuclear formula (rare)
c. Cases with a mixed formula
d. Cases with a combined cytological and chemical reaction (common).

3. Meningitis sympathica is a term which has been employed by Plaut and Schotmüller to designate the syndrome called by the French "méningite de voisinage," which arises as a result of a focus of inflammation situated near the dura mater: otitis media, mastoiditis, brain abscess, sinusitis, etc., giving rise by extension to a meningitis sympathica. The condition has been carefully

described by Strauss.[3] It is a reaction of defense on the part of the meninges. The symptoms are those of a serous meningitis, most of the cases being acute, although some run a subacute course and rarely others are hyperacute in development.

The cerebrospinal fluid is clear, or exceptionally slightly opalescent, and under increased tension. The cytological reaction varies from a slight to a moderate increase in cells, the formula being either lymphocytic or mixed in type.

The albumin and globulin are slightly augmented. The sugar and chlorides are normal or slightly diminished. The fluid is aseptic.

4. The aseptic meningitis form is recognized today as a sterile but often intense meningeal reaction which may be induced by the injection of a sterile foreign substance directly into the subarachnoid space; for example, the introduction of tetanic antitoxin, antipoliomyelitic convalescent or "immune" serum, even stovaine intraspinously or the prolonged injection of antimeningococcic serum during convalescence from epidemic meningitis. It would seem, however, that besides the cases following such provocative measures, there are certain rare forms in which aseptic meningitis may arise when no irritant has been injected into the subarachnoid space and which are probably due to some unrecognized toxemia or bacterial cause.

Whatever may be the cause, the meningeal symptoms are pronounced. The spinal fluid is under markedly increased tension and is opalescent or even frankly purulent. There is a marked cytological reaction present which is of a predominant polymorphonuclear type, but these polymorphonuclear cells are, however, characteristically well preserved and their nuclei are intact. The albumin and globulin reactions are moderate (two-plus) or marked (three-plus). The sugar is normal and no bacteria can be detected either in smear or culture.

II. Various Modified Types of Bacterial Meningitis

In this group may be included attenuated meningitis and rare cases of localized meningitis.

A. Attenuated meningitis presents a cerebrospinal fluid which contains bacteria, but for some reason the organisms are attenuated and a true meningitis is not produced. The spinal fluid is macroscopically clear or only faintly hazy, the cytological and chemical increase is variable and the sugar is apparently not greatly altered, although this point requires further investigation. Such

cases are probably not nearly so rare as was formerly thought, but are generally overlooked. The organism most commonly found is the pneumococcus, although the typhoid bacillus, the tubercle bacillus and the streptococcus may be encountered as well. In one of the cases of the series a Gram-negative bacillus of the influenza group was found.

Attenuated meningitis generally originates in the course of a septicemia, and at times may follow a septic exudative meningo-encephalitis, or even a tuberculous meningoencephalitis. Occasionally it is seen in hyperacute fulminating types of septicemia, notably those due to the pneumococcus and the meningococcus; and under such conditions the smears may contain numerous bacteria.

B. Localized meningitis ("méningite circonscrite" of the French) is a true meningitis of bacterial origin in which adhesions have shut off the process from the general subarachnoid space, either of the brain or of the spinal cord, or both. The spinal fluid has, therefore, the characteristics of a serous meningitis in the general subarachnoid space, while in the local focus the characteristics of an acute bacterial meningitis are present with the additional fact that this focus presents often a massive coagulation. This condition may arise during the course of various infectious diseases, such as typhoid fever, pneumonia, scarlatina, etc. It is, therefore, produced by various bacterial agents, among which may appear the meningococcus. In this series one spinal cul-de-sac case was due to the Bacillus pyocyaneus. Localized meningitis may also follow a meningitis sympathica or a trauma. It may also arise in the course of an exudative encephalitis as a localized and circumscribed meningoencephalitis, the bacterial cause being usually the staphylococcus, streptococcus or pneumococcus.

III. Acute Bacterial Meningitis or Acute Purulent Leptomeningitis

Acute bacterial meningitis may be grouped as follows:

A. Primary form (epidemic)

1. Meningococcus cerebrospinal meningitis

2. Pneumococcus cerebrospinal meningitis

B. Secondary form (non-epidemic)

1. Meningitis developing in an infectious disease and due to the organisms causing disease (exception to this last statement

must be made in the case of measles, acute rheumatic fever and possibly typhus fever, since their causative organisms are still doubtful):

Pneumonia	Scarlet Fever	Syphilis
Influenza	Measles	Tuberculosis
Erysipelas	Diphtheria	Anthrax
Epidemic Parotitis	Gonorrhea	Acute Rheumatic Fever
Typhoid and Typhus Fever	Bubonic Plague	Actinomycoses

2. Meningitis developing in the course of various septicemias and due to any of the etiological agents of the diseases in Group 1 and also to the streptococcus, the staphylococcus, colon bacillus and, rarely, other organisms.

3. Septic meningitis, secondary to a local infection and due to the microorganisms found in the skin or in the cavities of the body closely communicating with the cutaneous surface. The most common form is that due to otitis media, and mastoiditis. Less frequently it is due to infections of the face and scalp, to fractures of the skull, and to nasal, orbital, ocular and buccal infections; hence the most common causative bacteria are the streptococcus, the staphylococcus and the pneumococcus. Rarely it is due to the colon bacillus, Bacillus pyocyaneus, etc.

4. Unclassified forms due to Micrococcus catarrhalis, Micrococcus tetragenus, enterococcus, streptothrix, yeast, etc., some of which may be placed in Group 2, others in Group 3.

A. PRIMARY FORM (EPIDEMIC TYPE) OF ACUTE BACTERIAL MENINGITIS

1. Meningococcus Cerebrospinal Meningitis. The material for the conclusions drawn comprised 450 fluids from cases of meningococcus meningitis. Some of the more unusual physico-chemical data were completely lacking, and the literature has been consulted, in order to indicate briefly the complete cerebrospinal fluid findings in this disease.

Aspect. The fluid has diverse aspects depending on the stage of the disease. Typically it is a purulent liquid. In the first twenty-four hours the appearance is limpid, from the second to the fourteenth day or later it is purulent, while after the second week it is clear in over 55 per cent of cases. At times in unfavorable cases

the liquid is very thick, contains shreds of pus and will scarcely flow through the needle.

Color. During the very acute period the color varies from a milky white opalescence to a yellowish-green hue. As improvement begins, the color begins to diminish until it attains again the limpid aspect of the onset. Often, however, it retains a xanthochromic tinge, even when it is no longer cloudy.

Sediment and Network. In the early stage a yellowish-white or green pellicle of fibrin forms, which adheres to the side of the tube. Later yellow granules precipitate, and in very grave cases a thick sediment accumulates at the bottom of the container.

Pressure. The tension is increased in practically all cases. When the pressure is low, especially if the fluid is thick or purulent, an interruption of the communications between the ventricles and subarachnoid space is suggested. The actual pressure determinations vary between 300 and 650 mm. of water. Levinson[4] has observed a pressure of 800 mm.

The amount of fluid is considerably increased, and on puncture 25 to 40 c.c. are usually readily removed under pressure.

Freezing Point. This varies from $-52°$c. to $-64°$c. (Widal, Ravaut and Sicard[5]).

Hydrogen-Ion Concentration. This is slightly higher than normal, the P_H varying between 7.2 to 7.5 (Levinson).

Viscosity. This is 1.052 (Levy Valensky[6]).

Index of Refraction. This is augmented, 1.33512 to 1.33705 (Babes and Babes[7]).

Albumin and Globulin. The albumin content is greatly increased. The actual quantitative figures given by various authors vary considerably. Thus Comba[8] gives as low as 1.5 gms. in some cases; Nonne and Apelt[9] from 3.5 to 6.0 gms., and Wolf[10] from 7 to 8.5 gms. per liter. In general, in most fluids the amount of albumin equals or exceeds 3 gms. per liter.

Qualitatively, albumin and globulin show very marked increases by the usual tests during the height of the disease. Thus a three-plus and a four-plus albumin and globulin reaction was the most common in the cases collected.

There may be in some cases a persistence of an abnormally high albumin content of the fluid during convalescence after all clinical symptoms of the disease have disappeared. Thus Mestrezat[11] has observed this residual albumin content ranging from 0.7 to 1 gm. per liter in three patients.

Sugar. The meningococcus, by its fermentative action on glucose, causes a rapid disappearance of this substance from the cerebrospinal fluid. During the height of the disease the sugar content is greatly diminished and may be entirely absent. The quantity varies between 0.15 and 0.30 gm. per liter, with an average of 0.20 gm. per liter.

Qualitatively Fehling's solution shows this sugar diminution very well, and usually within twenty-four to thirty-six hours of the appearance of a purulent fluid no sugar can be detected by this test. The sugar reappears under serum therapy, as improvement begins, usually about the fifth to sixth day, although it may be later in severer cases, and generally never reappears in fatal cases. In patients in whom the disease terminates fatally, Fehling's solution is apt to turn a peculiar purplish hue (B. Riehl). The reappearance of sugar is, therefore, of great prognostic value; the earlier and more complete the return of the sugar, the better the outlook. On the other hand, the continued absence of sugar from the spinal fluid should be regarded with suspicion and as a cause for caution in prognosis, even when the other findings and symptoms indicate an amelioration in the severity of the disease.

Chlorides. The quantity of chlorides is normal or slightly lowered (Mestrezat, Achard,[12] Nobécourt and Voisin,[13] etc.), ranging from 6.3 to 7.0 gms.; the average value being 6.6 gms. per liter. As convalescence is established, the chlorides gradually reach normal values.

Total Nitrogen, Non-Protein Nitrogen, Urea, Creatinine, Creatine. Neal and Kahn[14] give the following values:

TABLE XXX

TOTAL NITROGEN, CREATININE AND CREATINE ETC., IN, MENINGOCOCCUS CEREBROSPINAL MENINGITIS
(Variations in Mgms. per 100 c.c.)

	Minim.	Max.	No. of cases	Average
Total Nitrogen	22.72	250	30	47.25
Non-Protein Nitrogen	13.00	136.25	23	21.93
Urea Nitrogen	3.66	53.28	26	9.25
Creatinine	0.326	0.595	5	0.476
Creatine	0.704	....	..	0.704

Lactic Acid. This substance is present in quantities ranging from 0.57 to 0.80 gm. per liter (Lehndorff and Baumgarten[15]).

Dry Extract. This is elevated from 13.5 to 16.8 gms. per liter (Mestrezat[11]).

Ash. This does not fall lower than 8 gms. In seven observations Mestrezat found values of 8.0 to 8.8 gms. per liter.

Permanganate Index. This is high, ranging from 5 to 7 (Levinson).[4]

Colloidal Gold Curve. The reaction occurs most pronouncedly in the meningitic zone, the greatest color change being produced in tubes 7, 8, 9 and 10. The curve, however, is usually a gradually rising type, beginning in dilutions of 1:40 to 1:80. A common type of reaction may be expressed numerically as 001122343; there are, however, marked variations from this, and it is difficult to fix a standard. At times the reactions extend to the colorless zone in tubes 9 and 10.

As improvement occurs, it is rather characteristic that the colloidal gold curve is gradually displaced to the left into the stronger concentrations, the number of tubes involved gradually diminishing until by the fourth to the sixth week of the disease only the first few dilutions are concerned.

Week of Disease	Curve
First	0111222222
Second	0011222333
Third	1112211100
Fourth	2221111000
Fifth	2221100000
Sixth	2100000000

Colloidal Benzoin Reaction. This reaction is variable, owing to the frequent presence of blood and the products of cytolysis, which cause irregular reactions not only involving the meningitic tubes 8 to 12 but also the syphilitic tubes 1 to 5. Hence various readings have been encountered in our series, such as 000222002220000 and 112202202222000.

Meningeal Permeability. This is always augmented to nitrates, from .045 to .055 gm. per liter of sodium nitrate. This permeability diminishes as improvement occurs.[55]

The permeability to iodides is augmented, but the results are more variable (Leri and Du Pasquier,[16] Sicard,[17] Cruchet,[18] etc.).

Cytology. The most striking feature of the fluid in epidemic meningitis is the pleocytosis which is almost invariably present.

This reaction consists of a great increase in cells, ranging from several hundreds to several thousands per cubic millimeter. The highest count in the present study was 10,000 cells. It is characteristic that at the height of the disease the leucocyte count is practically entirely polymorphonuclear, 96 to 98 per cent. The number of lymphocytes, although proportionately greatly diminished, is actually numerically increased. These polymorphonuclear cells, in the very acute period of the disease, are degenerated, deformed, with a contour sometimes invisible and a protoplasm pale and often homogeneous.

As improvement occurs, the fluid becomes less purulent, the number of cells diminishes and the percentage of polymorphonuclear leucocytes is gradually lowered, being replaced at first partly, later completely, by lymphocytes as convalescence is established and the meningococci disappear and the sugar reappears.

Bacteriology. In the spinal fluid smear the meningococcus occurs as a Gram-negative, biscuit-shaped diplococcus, mainly intracellular but also often extracellular.

The number, size and shape of the meningococci vary greatly. They are usually not numerous and are disseminated irregularly. In exceptional fluids they are encountered in every field, while in others they are not found, despite the examination of a large number of preparations. This latter occurrence is more frequent with the meningococcus than with any of the other organisms causing a purulent meningitis. Therefore, it may be stated that a purulent fluid in which the sugar is low and no organisms are found is very probably due to the meningococcus and should be so treated. The cases in which the meningococci are numerous and mainly extracellular are usually grave types of the disease. In mild forms of the disease and in those with late basal involvement the number of micrococci may also be extremely small. As improvement occurs, the meningococci diminish in number and become more and more intracellular.

Cultures. This microorganism is not easy to cultivate successfully. It is very sensitive to light and cold. For this reason the spinal fluid should be cultured within a very short time of its removal from the body. If this is unsuccessful, the enrichment method of keeping the fluid in the incubator for twenty-four to thirty-six hours at 37°c. may be tried. The best culture media are serum agar, blood agar and ascitic agar. Bouillon is diffusely clouded by the growth, milk is not coagulated, glucose and maltose

are fermented and cultural growth occurs at an optimum temperature of 37°c. and will not occur below 25°c.

Biochemical Properties. The agglutination tests with the respective antisera allow us to separate the parameningococcus from the meningococcus and to differentiate the types of the latter.

The precipitin bodies are present in the spinal fluid, and the Vincent-Bellot test is formulated on this basis. It is, however, not entirely reliable, but is of diagnostic assistance in cases in which the first puncture does not disclose any organism.

2. Pneumococcus Cerebrospinal Meningitis. This form of purulent meningitis is next in order of frequency of occurrence to that due to the meningococcus. It may occur rarely as a primary infection; in general, it is secondary, either to a pneumonia during evolution or after defervescence or to an otitis media. Less often it develops secondarily to a sinusitis, an ocular infection, a fracture of the skull, an appendicitis, a puerperal sepsis, or during typhoid fever, diphtheria, etc.

The present series comprised forty-five fluids from 33 cases of this disease.

General Appearance. The spinal fluid macroscopically is a purulent liquid, at first rather milky in appearance, and under marked increased tension. A xanthochromic tinge may be observed, but usually the fluid varies from a grayish-white to a yellowish-green hue. Fibrin is abundant and a fibrinous coagulum is rapidly formed.

Albumin and Globulin. The albumin and globulin content is high and is represented, in the majority of cases, by a very marked reaction (two- to four-plus).

Sugar. This is usually absent by Fehling's qualitative test, but it may be present in exceptional cases (one- or two-plus). Quantitatively, the value in one case was 0.192 gm.

Cell Count. This is greatly increased, the majority of the cell counts mentioned exceeding 300 cells, the maximum being 4042 cells per cubic millimeter. The differential cytology shows from 80 to 90 per cent or more polymorphonuclear leucocytes.

Chlorides. The chlorides in 2 cases (four fluids) ranged from 6.08 to 6.44 gms. per liter (Mestrezat[11] gives 6.3 to 7.6 gms. per liter).

Protein. The protein ranged from 2.34 to 3.91 gms. per liter in one fluid, after serum showing 12.81 gms. (Mestrezat gives 2.0 to 7.0 gms., with exceptional values of 11.60 gms.)

The pneumococcus was recovered in each patient's fluid. Typing was carried out in 22 cases, with the following results:

Type 1	8 cases	Type 3	8 cases
Type 2	4 cases	Type 4	2 cases

The organism in direct smears is fairly typical, occurring usually as an elongated Gram-positive diplococcus, intra- and extracellular. It not infrequently occurs in short chains, and in some cases the organism reacts indefinitely to the Gram stain. However, on cultivation the typical morphology is observed and the bile solubility test, fermentation reactions with inulin and the inoculation of a mouse serve to identify the organism.

B. SECONDARY (NON-EPIDEMIC) FORM OF ACUTE BACTERIAL MENINGITIS

1. MENINGITIS DEVELOPING IN AN INFECTIOUS DISEASE. (a) *Typhoid Bacillus Meningitis.* A purulent meningitis due to the typhoid bacillus may occur as a unique localization in the course of a septicemia without any manifestation of classical typhoid fever. Usually, however, it develops during the course of the disease, either at the onset or at the height of the infection.

The spinal fluid is under increased tension, opalescent or may have a frankly purulent aspect. The albumin and globulin are augmented, as are also the cells with the predominance of the polymorphonuclear variety which, if recovery occurs, is replaced by a lymphocytosis that may persist for a long period. The bacillus of Eberth is found either in a hanging drop as a motile bacillus or on staining the spread from centrifugation; but to be identified, it should be cultured and tested by agglutination reactions. For successful cultures a large amount of spinal fluid must be employed. The cultures when grown are tested by agglutination with antityphoid serum, with blood of a proved typhoid fever case, with the blood of the patient and even with the cerebrospinal fluid of the patient. This rigorous identification is necessary to distinguish the typhoid from the paratyphoid bacillus (Chauvet).

The cerebrospinal fluid agglutinates the typhoid bacillus and also, in a dilution slightly greater, the bacillus isolated from the patient by culture. The agglutination power of the fluid is low (1:20 to 1:40), but it is important and serves to distinguish the amicrobic meningeal states from the true typhoid meningitis (Chauvet).

(b) *Influenza Bacillus Meningitis.* This form of purulent meningitis develops usually in patients with a grippe syndrome, including a bronchopneumonia. In the present series there were eighty-one fluids from 19 cases, and in each of these the diagnosis was established by isolating the influenza bacillus.

The macroscopical appearance of the fluid is slightly turbid or opalescent at first, later distinctly cloudy and of a yellowish color. The albumin and globulin content is increased, the predominant values being a two-plus and a three-plus. The sugar is usually absent qualitatively by Fehling's reaction; exceptionally it may persist, and the fluid may give a one- or two-plus or even rarely a three-plus reaction during the entire course of the disease. The cells are greatly increased, the counts ranging from 225 to 3260 cells per cubic millimeter, with an average of 90 per cent polymorphonuclear leucocytes. The colloidal gold curve is similar also to that of epidemic meningitis, as is the collodial benzoin reaction (four fluids, 1 case). The microorganisms appear in smears as fine Gram-negative bacilli or coccobacilli, usually extracellular. At times they are atypical and appear in long, thread-like forms. On culturing the fluid on blood agar, the microorganisms develop their typical morphological character. A few quantitative studies gave the following results: albumin, 0.40 to 0.85 gm. per liter; protein, 3.06 to 4.49 gms. per liter; sugar, 0.14 to 0.19 gm. per liter; chlorides, 6.44 to 7.25 gms. per liter (2 cases); total nitrogen, 51.50 to 138.75 mgms. per 100 c.c. (3 cases), and urea, 6.25 mgms. per 100 c.c. (1 case).

(c) Meningitis due to the tubercle bacillus is discussed on page 339. Syphilitic meningitis is described elsewhere (see index). The acute bacterial meningitis complicating erysipelas, scarlet fever and measles usually has the streptococcus as the etiological agent, and often occurs as a septic form. The meningitis of epidemic parotitis is spoken of under the heading of that disease. The remaining forms are all very rare and will not be discussed here.

2. Meningitis developing in the course of various septicemias, and due to any of the etiological agents of the diseases in Group 1 (p. 320), will conform in symptomatology to primary meningitis due to these agents.

3. Septic Meningitis. (a) *Streptococcus Meningitis.* This form of meningitis is usually secondary to a local infective focus in the face, scalp or one of the cavities of the skull, especially the ear or nose. It may also develop during streptococcus septicemia.

The present tabulations included fifty-six fluids from 37 cases, in each of which a streptococcus was found.

Macroscopical Appearance. The cerebrospinal fluid is at first not so cloudy in appearance as in epidemic meningitis. It is frequently only slightly hazy for the first few days. The amount is increased and the pressure is high. The freezing point varies between −53°c. and −62°c. (Mestrezat and Monad).

Chemistry. The albumin and globulin are markedly increased, three- and four-plus reactions being very common. The sugar content of the fluid was greatly reduced in the majority of the examinations as judged by the negative qualitative Fehling test. However, streptococcus meningitis is less characteristic in this respect than meningococcus meningitis, and it is not unusual to find a slight one-plus or even a moderate two-plus reaction persisting until well into the height of the disease.

The total nitrogen ranged between 23.38 and 86.30 mgms. per per 100 c.c. in 2 cases; the non-protein nitrogen, 18.08 mgms. in 1 case, and urea nitrogen, 11.10 mgms. per 100 c.c. in 1 case (determinations of J. B. Neal and R. L. Kahn[14]). A few other determinations are available in the literature: albumin, 1.08 (Mestrezat[11]) to 4.0 gms. (Rous[19]) per liter (2 cases); chlorides, 6.5 to 7.5 gms. per liter (Mestrezat, Monad); alkalinity of ash (Na_2Co_3), 1.60 gms. per liter, and no acetone or ammonia (Mestrezat, 1 case).

The cells are greatly increased at the height of the disease, but apparently are not so numerous as in meningococcus meningitis during the first few days. Thus there were observed cell counts of only 100 to 400 per cubic millimeter even several days after the onset. The cell count may reach the very high figures of 12,000 to 24,000 cells per cubic millimeter; usually, the polymorphonuclear cells predominate in the percentage of 80 to 99 of the total. At times, however, the lymphocytes may be proportionately very high (65 per cent of the total). The colloidal gold reaction presents a meningitic type of reduction.

Bacteria. The streptococcus occurs in smears of the fluid as a Gram-positive coccus arranged either as a diplococcus or in short chains, usually extracellular but often intracellular as well. Cultures on blood agar serve to differentiate the type of streptococcus found. In this series, when classified, they were: Streptococcus hemolyticus 18, Streptococcus viridans 3, Streptococcus mucosus 1. The Streptococcus putridus has also been rarely reported.

(b) *Staphylococcus Meningitis.* This organism appears at times as a causative agent of purulent meningitis. It usually originates from an injury to the scalp or skull, but it may occur during a staphylococcus septicemia.

In the present series there were 12 cases of staphylococcus meningitis presenting 25 individual spinal fluid examinations. In these cases the fluid was always purulent, cloudy, yellowish-gray or green. The tension was high until the development of a basilar meningitis. The albumin and globulin were greatly increased, presenting a three-plus or four-plus reaction. The sugar was much diminished or altogether absent by Fehling's test in the majority of cases. In a number, however, a one-plus or even a two-plus reduction persisted until the more advanced stages of the disease. The polymorphonuclear cells were greatly increased and much degenerated. The staphylococci appeared in smears as Gram-positive cocci arranged in clusters, isolated as diplococci, or in very short chains. They may be intra- or extracellular. The organism may at times be Gram-negative.

(c) *Colon Bacillus Meningitis.* This type of meningitis originates during a colon bacillus septicemia, a pyelitis, or rarely from an accidental contamination during lumbar puncture, etc. In this series there were thirty-six fluids from 4 cases, in each of which the colon bacillus was found as a Gram-negative bacillus on smear and culture. The spinal fluid presents typically a very green color, and may have the characteristic odor, which, however, is more obvious on post-mortem examination of the brain. The albumin and globulin are usually four-plus and the sugar absent by Fehling's test.

4. Rare Forms of Acute Bacterial Meningitis (Included in the Present Tabulation). (a) *Micrococcus Catarrhalis Meningitis.*[20] One case is included in the present tabulation. The spinal fluid was cloudy, showed a large increase in cells (95 per cent polymorphonuclear leucocytes), a two-plus or three-plus albumin and globulin, two-plus or three-plus Fehling's reaction and on smear Gram-negative diplococci, intra- and extracellular. Cultures showed a vigorous growth of the organism which could be differentiated from the meningococcus by its growth at ordinary temperature, fermentation reactions with sugars, the type of colonies and agglutination tests.

(b) *Friedlaender's Bacillus Meningitis.* One case is included, with a cloudy fluid, showing a great increase in cells, a three-

plus albumin and globulin, a negative Fehling's reaction and a Gram-negative, short diplococcus or coccobacillus, intra- and extracellular.

(c) *Streptothrix Meningitis.*[20] One case is included showing a cloudy fluid with a large increase in cells (polymorphonuclear leucocytes), a four-plus albumin and globulin reaction, a negative Fehling's reaction and on smear a gramophilic coccus and bacillus; on culture under anaerobic conditions a streptothrix was obtained.

(d) *Yeast Meningitis.*[21] One case is included in which 92 fluids were examined, all showing this fungus.

(e) *Bacillus Pyocyaneus Meningitis.* The records include 2 cases in which bacillus pyocyaneus was found.

iv. Various Forms of Acute Meningoencephalitis

An encephalitis may originate in almost any of the infections. It appears most commonly in influenza, measles, pertussis, scarlet fever, pneumonia, erysipelas, diphtheria and typhoid fever. The cerebrospinal fluid is clear, usually under increased tension, the albumin and globulin content is increased and there is a lymphocytosis of a variable intensity depending upon the extent of the meningeal involvement. The cells are usually only slightly increased. In the present collection of fluids there were 7 cases of acute encephalitis complicating measles, 3 cases of acute encephalitis complicating pneumonia and 4 cases of acute encephalitis of unmentioned origin.

A. Acute Encephalitis Complicating Measles. The fluid was clear in all cases; the tension when mentioned was specified as being increased. The albumin and globulin were negative in four fluids, one-plus in three and two-plus in one. The cell counts were 0, 2, 10, 10, 30, 45 and 87. The mononuclears were specified as 98 per cent in one case. Fehling's test showed a three-plus reaction. The gold chloride test performed in 3 cases showed a weak luetic curve in all.

Quantitative protein estimations were made in 2 cases showing 0.90 to 0.93 gm. per liter. Quantitative sugar determinations gave values of 0.64 to 0.83 gm. per liter in two fluids.

B. Acute Encephalitis Complicating Pneumonia. There were three fluids, all presenting a clear appearance. The globulin was negative in two, and two-plus in one fluid; Fehling's reduction was normal. The cell count showed 0, 10 and 23 cells per cubic

millimeter. The colloidal gold curve showed one negative and one positive curve in the luetic zone.

C. Acute Epidemic Encephalitis. The spinal fluid in this disease shows alterations of an extremely variable type, not only in different cases, but also during the course of the same case (Kraus and Pardee[22]). The information which permitted the drawing of the conclusions in the present study was based on the tabulation of 300 fluids. It is evident that much more investigative work remains to be performed before our knowledge is at all complete on the characteristics of the cerebrospinal fluid in this disease.

Macroscopical Appearance. The spinal fluid in epidemic encephalitis is a clear, limpid and colorless liquid. It does not have a ground-glass appearance, rarely a xanthochromic tinge, and very seldom indeed a fibrin reticulum. A bloody fluid is occasionally encountered.

Cerebrospinal Fluid Pressure. The pressure is either normal or slightly to moderately elevated. A few exact measurements of the pressure have been made. Thus a tension of 50 centimeters of water in one case and 20 to 30 centimeters by the manometer of Claude in several others are recorded (Van Boeckel, Bessemans and Nelis[23]).

The quantity of fluid is evidently increased, and 15 to 30 c.c. may generally be obtained.

Protein. Kraus and Pardee[22] noted an increase of protein in 72 per cent of the cases tabulated in the 1921 study of this disease by the Association for Research in Nervous and Mental Disease.

In the present investigations, the albumin test was performed in 186 fluids and the globulin in 263 fluids. The results showed that the albumin was increased in 65 per cent and the globulin in 56 per cent of the fluids examined and that this augmentation was practically limited to a slight one-plus and a moderate two-plus reaction.

Quantitatively the protein determinations were made on sixteen fluids, and ranged from a minimum of 0.47 gm. to a maximum of 1.34 gms. per liter, with an average of 0.82 gm.

Sugar. Netter and later Dopter[24] first observed that an increase in the amount of sugar in the cerebrospinal fluid in epidemic encephalitis occurred in the vast majority of cases. Quantitatively this sugar ranged from 0.67 to 1.06 gms. per liter, with an average of 0.75 gm. This average is high if the figures 0.45 gm. to 0.58

gm. per liter are accepted as the normal, as established by Deniges, Navratski, Sicard, Anglada, Mestrezat,[11] etc. Kraus and Pardee[22] found figures ranging from 0.62 gm. to 0.95 gm. per liter in twelve examinations in this disease.

In the present series, fifteen fluids from 11 patients were tested quantitatively. The determinations ranged from a minimum of 0.49 to a maximum of 1.00 gm. per liter, with an average of 0.69 gm. Of the fifteen specimens, eleven showed values above the normal.

Qualitatively, examination with Fehling's solution gave a three-plus reaction in all the fluids (169) examined, with the exception of five.

Chlorides. There is little in the literature on the chloride content of the cerebrospinal fluid. Bonnard,[25] and Moriez and Pradal[26] consider the chlorides normal or slightly increased. In the present series, the chlorides were determined in fifteen fluids and presented values ranging from 6.06 gms. to 8.50 gms. per liter, with an average of 7.26 gms. This, then, corroborates the fact that the chlorides are usually normal, although they may be increased. It also seems to indicate that they may in exceptional cases be slightly diminished.

Colloidal Gold Reaction. Kraus and Pardee[22] found the colloidal gold curves changed in 100 of 120 cases included in their tabulated study (87 per cent). The type of curve varied considerably, but there was a tendency to a color change in the high and medium concentrations of the cerebrospinal fluid. Changes in the low concentrations did not occur alone, but were encountered when the medium and high concentrations were altered. Positive curves were found as late as the twenty-first month after the onset of the disease.

The curves collected in the present tabulation showed a general confirmation of these statements with, however, minor differences. The reaction was performed in 26 fluids. In 5 the result was negative and in 21, or 86 per cent, there was some color change. In the majority of these 21 cases, namely, in 17, the reaction was confined to the high and medium concentrations (luetic zone), in 2 of which it extended into the low concentrations. In 2, the curve was confined to the mid-zone and in 3 others it was limited to the meningitic zone. In 7 of the fluids with a luetic zone (strong concentration) curve, the reaction was so slight as to be almost negligible. The results, then, showed no characteristic reaction,

the most frequent curve being one in the luetic zone, the next a negative curve, while not infrequently the reaction extended into the meningitic zone.

Colloidal Benzoin. This reaction has been found negative in epidemic encephalitis by Guillain and Lechelle[27] (9 cases), Duhot and Crampon[28] (6 cases), Bregi[29] (13 cases), and Rabeau[30] (10 cases). This test has been performed on only three of the fluids in the present series and was negative in all.

Bordet-Wassermann Reaction. The complement fixation test has been found negative in 71 cases of the present study. This is confirmatory of previous reports. However, a few rare cases are recorded in which the reaction has been positive in non-syphilitic patients (Achard and Leblanc,[31] etc.), but none of this character was encountered in the present investigation.

Cytology. In many of the early observations on the spinal fluid in epidemic encephalitis, the cell count was considered entirely normal. Later studies have shown this viewpoint to be incorrect.

Table XXXI

Quantitative Sugar, Protein and Chlorides in Epidemic Encephalitis (Expressed in Grams per Liter)

	No. of spinal fluids	Min.	Max.	Aver.
Sugar	15	0.49	1.00	0.69
Protein	16	0.47	1.34	0.82
Chlorides	15	6.06	8.50	7.26

Table XXXII

Qualitative Albumin and Globulin Tests in Epidemic Encephalitis

	No. of spinal fluids giving various degrees of reaction					Total No.
	Negat.	1+	2+	3+	4+	Tested
Albumin	64 (35 per cent)	64 (35 per cent)	50 (27 per cent)	4 (1.5 per cent)	4 (1.5 per cent)	186
Globulin	117 (44 per cent)	82 (32 per cent)	58 (22 per cent)	4 (1.2 per cent)	2 (0.7 per cent)	263

Table XXXIII

Cell Count in Epidemic Encephalitis

Total number of cell counts	162
Minimum cell count	0 cells per cu. mm.
Maximum cell count	900 cells per cu. mm.
Average cell count	56 cells per cu. mm.

DIFFERENTIAL COUNT

Total number of differential counts	67
Minimum percentage of lymphocytes	60 per cent
Maximum percentage of lymphocytes	100 per cent
Average	96 per cent

RELATIVE DEGREE OF CELL INCREASE

Under 10 cells per cu. mm	43 per cent of the fluids
Under 50 cells per cu. mm	72 per cent of the fluids
Under 100 cells per cu. mm	85 per cent of the fluids
Under 200 cells per cu. mm	95 per cent of the fluids

Van Boeckel, Bessemans and Nelis,[23] in a recent publication, express their conclusions by saying that the cellular reaction is feeble and often insignificant, the number of cells ranging from 10 to 100. Counts above 150 are exceptional. Several French investigators[32] have remarked the fact that a "dissociation albumino-cellulaire" often occurs, in which the quantity of albumin is proportionately inferior to the cellular content of the fluid. Occasionally an inverse dissociation has been encountered. The cellular reactions have a tendency to be most elevated at the onset and for the first few days, then to subside rather rapidly; but they may be re-elevated due to a relapse in the disease (Netter). One of the most extensive tabulations on the subject is that of Kraus and Pardee,[22] who collected the results in 260 cell counts.

In the present study the cell counts in 162 cerebrospinal fluids were tabulated. In 70, or 43 per cent, of these fluids the cell count was within normal limits, less than ten cells per cubic millimeter; in 117, or 72 per cent, there were less than fifty cells per cubic millimeter; in 138, or 85 per cent, less than 100 cells per cubic millimeter, and in 154, or 95 per cent, less than 200 cells. In only 6 fluids did the count exceed 300 cells. The highest cell count was 900 cells; the average was 56 cells. The average weekly counts for the first three weeks showed a gradual rise, 40, 61 and 66.

The relative percentages of lymphocytes and polymorphonuclear leucocytes specified in sixty-seven fluids showed over 90

per cent lymphocytes in about 86 per cent of the fluids examined. The lowest percentage of lymphocytes was 60 per cent and the average 96 per cent.

D. Post-Encephalitic Syndromes. Sixteen fluids from the same number of patients were tabulated. The fluids were clear, at times under increased pressure. The albumin and globulin were normal when mentioned, except in 2 cases where a one-plus reaction was encountered. Fehling's reaction was normal. Quantitative sugar determinations in 3 cases showed 0.58, 0.64 and 0.68 gm. per liter. Chloride determinations in 2 cases gave 7.10 gms. and 7.86 gms. per liter.

The colloidal gold reaction was performed in 11 cases. In one case the reaction was negative, in 4 it showed a very low luetic curve (1111000000), in 3 the reaction was mid-zone in position (0002211000 0002221100, 0012211000), while in 2 the curve was meningitic in character (0002343320).

Acute Poliomyelitis

The epidemic of acute poliomyelitis in 1916 permitted a fairly accurate determination of the cerebrospinal fluid formula in the acute period of the disease, so far, at least, as the routine examination was concerned. The present study includes the tabulated results in 508 fluids of this disease.

Macroscopical Appearance. The cerebrospinal fluid in poliomyelitis is a clear, limpid, colorless liquid which has often a ground-glass appearance by transmitted light. It is not unusual to note fibrin-web formation on standing. In the preparalytic stage the fluid may have at times a distinctly hazy opalescence. Very rarely, indeed, is it hemorrhagic or xanthochromic, and the vast majority of bloody fluids encountered are probably due to technical accidents in performing the puncture.

Pressure. The pressure is increased to a moderate or marked extent in the preparalytic stage, returning to normal as the acute symptoms disappear. The few figures available on the actual pressure indicate a range in tension of between 300 and 700 mm. of water. Quantitatively the fluid is evidently increased, and 20 to 30 c.c. or even more are readily obtained.

Protein. The albumin and globulin are usually definitely increased in the vast majority of cases. They are represented by a slight (one-plus) to a moderate (two-plus) increase, the former

being the most common. Occasionally a three-plus or four-plus reaction occurs. The augmentation in albumin and globulin persists after the cell count has returned to normal and, in exceptional cases, especially cases of polyneuritis, even to the fourth or sixth week of the disease.

Quantitatively in 60 cases the albumin ranged from 0.22 gm. to 0.85 gm. per liter, with an average of 0.30 gm. (by the Sicard-Canteloube albuminometer[33]).

Quantitatively the total protein was determined in fifteen fluids and showed a minimum of 0.323 gm. per liter and a maximum of 2.50 gms. per liter, with an average of 0.816 gm.

Sugar. The reduction of Fehling's solution qualitatively showed almost constantly a high normal (three-plus) reduction. Quantitatively the sugar was determined in 31 cases and ranged from a minimum of 0.40 gm. to a maximum of 1.06 gms. per liter, with an average of 0.66 gm.

Chlorides. The chlorides are considered by Peabody, Draper and Dochez[34] to be normal. In this series the chlorides were determined in fourteen fluids and showed a range of 6.62 to 7.50 gms. per liter, with an average of 7.01 gms.

The total nitrogen, non-protein nitrogen, urea nitrogen, creatinine, and creatine are shown in the following table (Neal and Kahn[14]):

TABLE XXXIV

TOTAL NITROGEN, CREATININE AND CREATINE, ETC., IN ACUTE POLIOMYELITIS

	Number of fluids	Variations per 100 c.c.		
		Minimum, mgms.	Maximum, mgms.	Average, mgms.
Total nitrogen	24	16.37	34.00	22.57
Non-protein nitrogen	16	8.91	24.78	15.71
Urea nitrogen	17	5.06	26.6	12.50
Creatinine	22	0.27	0.609	0.40
Creatine	11	0.19	0.495	0.45

Permanganate Index. This index was slightly above the normal, averaging 1.5 to 2.5 (Levinson[4]).

Cytology. The number of cells varies considerably, according to the day on which the examination is made. In the preparalytic stage the cells are moderately to markedly increased, while in the

first week of paralysis a slight to moderate increase is the common finding. Thus in a series of 500 fluids Neal[14] found that twenty-three, or 4.6 per cent, showed no increase; 211, or 42 per cent, a slight increase; 158, or 31 per cent, a moderate increase, and 21 per cent a great increase. The predominant change is, then, a slight to moderate increase.

The results of 117 cell counts in the present series are shown in Table XXXVI, indicating a range of 20 to 1800 cells in the first week and of 12 to 567 in the second week. It is noticeable that the cell count gradually returns to a normal figure by the fourth week of the disease, although considerably elevated counts may occur as late as the seventh week in exceptional cases. The average cell count in this series was 58.

Differential Cytology. In the preparalytic stage the polymorphonuclear cells are said by some writers to constitute sometimes from 80 to 90 per cent of the total (Draper, Peabody and Dochez). On the contrary, Neal found this reaction exceptional. In her study, the polymorphonuclear cells predominated in only 39 of 2000 fluids examined on various days, from the second to the twenty-seventh. She therefore considers that this type of cytological response is quite as likely to occur in any part of the acute stage as in the first few days of the disease, and that it represents a special type of reaction.

In the paralytic stage the predominating cell is of the mononuclear type, which represents from 80 per cent to 100 per cent of the total and is accompanied by a variable proportion of endothelial and polyform cells.

There seems to be little proof of a definite relation between the cell count or the chemistry of the fluid and the fatal outcome of the disease, or, indeed, between the extent or prognosis of the paralysis. The higher cell counts may have a relation to the "intensity of the meningeal phenomena" (Batten), and this seems probable and reasonable. If distinct meningeal symptoms are present, the non-paralytic cases "appear" to have the same cytological and chemical reactions as the paralytic cases.

Colloidal Gold Reaction.[35] This test was performed in about 200 fluids of the present series. The cerebrospinal fluid in this disease very constantly produces a reduction in the colloidal gold solution in the strong concentrations, giving a low luetic curve.[35] This reduction occurs in dilutions of 1:10 to 1:320 and reaches only the blue or purple zone, being typically represented numerically by

a curve of 1122100000. It is one of the most persistent of the pathological findings in the fluid, as it remains elevated in the majority of cases beyond the fourth week of the disease. It has no close relation to the degree of cytological reaction in the fluid.

Colloidal Benzoin Reaction. This test was performed in fifty spinal fluids from 23 cases. A reaction was observed in all except one fluid during the first three weeks. The precipitation[36] was encountered with marked constancy in the lower dilution of the meningitic zone, with precipitation in tubes 6, 7, 8, 9 and 10. Occasionally tube 11 and rarely tube 12 showed some change. There seems to be a rough but definite relation between the amount of albumin and globulin in the fluid and the colloidal benzoin precipitation.

Bordet-Wassermann Reaction. This test was always negative when mentioned (70 cases in this series).

Table xxxv

Quantitative Albumin, Sugar and Chlorides in Acute Poliomyelitis (in Grams per Liter)

	No. of spinal fluids	Min.	Max.	Aver.
Albumin	26	Less than 0.22	0.86	0.30
Chlorides	14	6.62	7.50	7.01
Sugar	31	0.40	1.06	0.66

Table xxxvi

Cell Count in Acute Poliomyelitis

Total number	117
Minimum cell count	0 cells per cu. mm.
Maximum cell count	1800 cells per cu. mm.
Average cell count	58 cells per cu. mm.

Relative Degree of Cell Increase

Under 10 cells per cu. mm.	15 per cent of the fluids
Under 50 cells per cu. mm.	54 per cent of the fluids
Under 100 cells per cu. mm.	76 per cent of the fluids
Under 200 cells per cu. mm.	88 per cent of the fluids

Tuberculous Meningitis

The cerebrospinal fluid in tuberculous meningitis presents a characteristic formula, when the chemical, cytological and bacteriological findings are all taken into consideration. Many variations are encountered, however, depending on the stage of the disease when the cerebrospinal fluid is examined and also on the extent of the formation of tubercles in the meninges. Rarely no cerebrospinal fluid[37] can be obtained, owing to massive tubercle formation at the site of the spinal meninges, causing a dry subarachnoid space.

Macroscopical Appearance. The spinal fluid is typically a clear, limpid, transparent liquid which is very rarely frankly cloudy, but may present at times a faint haziness. In the present series of 224 fluids the aspect was clear in all except 12, in which a hazy appearance was noted.

The cerebrospinal fluid in this disease is characteristically a colorless liquid. It exhibits only rarely a true hemorrhagic character; most of the bloody fluids encountered from time to time are the result of trauma at the time of lumbar puncture. The liquid, however, may not infrequently have a peculiar yellow or xanthochromic appearance. This has been observed by Netter (1898), Widal, Sicard, Bard, Rosenthal and many others, but only in adults. Apparently the origin of this color is chiefly from blood pigment (oxyhemoglobin). Biliary pigment has also been recognized by spectroscopical examination (Paupe[38]). The frequency with which xanthochromia is encountered seems to vary. Ramond[39] noted it in 4 out of 14 cases.

In the present series of 224 fluids a yellow coloration of the fluid was noted in only 7. In these patients the age varied from four months to forty-nine years, 4 of them being under seven years. These fluids were obtained from the eighth to the nineteenth day of the disease. It would seem, therefore, that xanthochromia in tuberculous meningitis may occur at any age.

Sediment and Network. There is rarely seen any true sediment in tuberculous meningitis. If the spinal fluid is allowed to stand undisturbed for several hours, a very fine network of fibrin, resembling a cobweb, forms, appearing to be suspended from the surface of the fluid and waving to and fro with the movements of the tube. This reticulum is so fine that it may pass unnoticed and later may fall to the bottom of the tube.

Tension. The pressure is considerably elevated in nearly all of the cases. It is apt to be higher during the earlier stage of irritation than later in the stage of paralysis. The actual pressure ranges from 300 to 700 mm. of water. As the pressure indicates, the quantity of spinal fluid is considerably augmented and on puncture 20 to 40 c.c. are readily obtained and under such distinct pressure that the liquid spurts from the needle.

Density. The specific gravity varies apparently from 1.008 to 1.012 (Ley,[40] Dircksen,[41] Halpern and Landau,[42] etc.).

Viscosity. This varies between 1.0693 and 1.0694 (Fuchs and Rosenthal[43]).

Conductibility. In seven determinations the values ranged from .0097 to .0225, with an average of .0127 (Fuchs and Rosenthal[44]).

Freezing Point. The freezing point is lowered (Sicard, Widal, Ravaut,[45] etc.). Lautier,[46] in 79 per cent of 43 cases, found the freezing point to vary between -44°c. and -64°c. with an average of -49°c.

Hydrogen-Ion Concentration. This averages P_H 7.4 to 7.6 (Levinson[4]).

Protein. The albumin and globulin content of the spinal fluid is increased in tuberculous meningitis. This increase is slight during the first few days, but is rapidly augmented as the disease advances, and is represented by a moderate (two-plus), marked (three-plus) or occasionally a very marked (four-plus) reaction. In the tabulation of the fluids collected in this study, it will be seen that out of 136 examined for albumin, 106, or 77 per cent, gave a two-plus or three-plus reaction, and of 163 tested for globulin, 114, or 70 per cent, showed a similar increase.

Quantitatively the amount of albumin found by various investigators seems to range between 0.50 and 3.2 gms. per liter (Mestrezat,[11] Comba,[8] etc.). Exceptionally, high values have been noted, such as 5 gms. by Mestrezat[11] and 9 gms. by Pfaundler.[47] The unusually high quantities generally relate to fluids removed from adult patients within twenty-four hours of death. It seems that at this time the albumin content may be considerably augmented.

The quantitative protein was determined in thirty-four fluids in this series and varied between 0.40 and 8.80 gms. per liter. The tabulations of the protein by weeks shows that the average remained closely around 2.64 gms. per liter. In only two fluids was less than 1 gm. observed. The unusual value of 8.8 gms. in

one fluid is one of the highest noted, except that previously recorded by Pfaundler.

Sugar. The sugar content of the fluid shows a change as soon as the distinct clinical symptoms of the disease are established. This change is a diminution of the sugar content which becomes progressively more pronounced as the disease advances, until the sugar is reduced to traces and qualitatively the reaction is negative.

At the beginning of the disease a three-plus reduction of Fehling's solution is not infrequently encountered, but this soon changes to a two-plus, a one-plus, or a negative reaction as the disease advances, the latter being the most typical, as Table XXXVIII on page 344 will show. Thus of 153 spinal fluids tested, 111, or 72 per cent, gave a one-plus or a negative reaction. It will be noted, too, that the frequency of the three-plus and two-plus reactions generally decreased as the disease progressed. Quantitatively the actual sugar content of the liquid, as given by various authorities, varies between 0.11 and 0.31 gm. per liter, with an average of 0.21 gm. (Comba,[8] Sicard and Langwelt,[48] Clemenceau,[49] etc.). In the present study and tabulations, thirty-three fluids were examined quantitatively for sugar, and it was found that the amount was distinctly diminished, usually to a moderate or marked degree. The minimum quantity recorded is 0.10 gm. and the maximum 0.50 gm., the average being 0.27 gm. per liter.

Chlorides. The chlorides in tuberculous meningitis are lowered, according to observations by Deniges and Sabrazes,[50] Widal,[43] Sicard and Monod,[51] Aporti,[52] Halpern and Landau.[42] Mestrezat[11] gives figures ranging from 4.7 gms. to 6.4 gms. per liter, and considers this as one of the pathognomonic findings in tuberculous meningitis. In the present series of fluids, 31 presented quantitative chloride determinations, the results ranging from a minimum of 5.0 gms. to a maximum of 6.87 gms. per liter, the average being 6.25 gms. This latter figure is distinctly lower by approximately 1 gm. than the average chloride content of the normal cerebrospinal fluid.

Total Nitrogen, Non-Protein Nitrogen, Creatinine, Etc. The following figures are available (Neal and Kahn[14]):

Total Nitrogen: In 11 fluids it ranged from 20.86 to 34.50 mgms. per 100 c.c. Non-Protein Nitrogen: In 5 fluids it ranged from 12.82 to 25 mgms. per 100 c.c. Creatinine: In 2 fluids it ranged from 0.487 to 0.765 mgm. per 100 c.c. Creatine: In 2 fluids it ranged from 0.563 to 0.735 mgm. per 100 c.c. Urea Nitrogen:

Deniges and Sabrazes[50] found 15 mgms.; Frenkel-Heiden,[53] 42 mgms., and Neal in 8 cases determined 4.54 to 14.18 mgms. per 100 c.c. Ammonia is absent.

Acetone. It is entirely absent or evident in only light traces.

Phosphates. These vary from 0.034 to 0.049 gm. per liter (Apelt and Schumm[54]).

Lactic Acid. It is positive in 9 cases, to the amount of 1.40 gms. per liter (Lehndorff and Baumgarten[15]); Mestrezat[11] noted 0.47 to 1.66 gms. per liter.

Ash. Tuberculous meningitis shows a diminution in the mineral content of the fluid; hence the ash is lowered, ranging from 6.9 gms. to 8.5 gms. per liter, with an average of 7.44 in 11 observations (Mestrezat[11] and Deniges).

Permanganate Index. This varies from 2.1 to 3.0 (Levinson[4]).

Meningeal Permeability. Permeability to nitrates is increased. They are augmented greatly, from .050 to .080 gm. per liter (Mestrezat[11]), and from .030 to .080 gm.[55] in the present study. Permeability to iodides is also increased.

Cytology. The characteristic cytological reaction in the cerebrospinal fluid in tuberculous meningitis is a moderately marked increase of cells of predominantly lymphocytic type.

The cell count varies somewhat, Fontecilla and Sepulveda[56] giving an average of 100 cells per cubic millimeter, with extremes of a minimum of 8 and a maximum of 1000 cells. The cellular increase rarely reaches the average high counts found in purulent meningitis.

In the present study the cell counts have ranged from a minimum of 0 cells per cubic millimeter to a maximum of 1000 cells in a total of 131 cell counts performed. The average cell count was 112. Only five spinal fluids gave a normal number of cells; approximately 68 per cent of the fluids showed a cell count under 100 cells per cubic millimeter, and only 6 per cent showed a cell count over 300. Therefore, it may be said that the cell count in tuberculous meningitis very seldom exceeds 300 cells per cubic millimeter and that in the vast majority of cases (85 per cent) it is under 200 cells per cubic millimeter.

Differential Cytology. In the cerebrospinal fluids in which the relative percentages were specified, the lymphocytes were proportionately in the majority, except in 5 cases where the polymorphonuclear leucocytes were numerically superior (70 per cent to 80 per cent of the total count). Fontecilla and Sepulveda[56]

give the habitual formula as 62 per cent lymphocytes, 8 per cent large mononuclear leucocytes and 30 per cent polymorphonuclear leucocytes. The limited number of examinations performed in our series does not diverge greatly from this.

Colloidal Gold Reaction. The fluid in tuberculous meningitis very constantly reduces gold chloride solution. The reaction varies somewhat in different cases, but in general it is characterized by a curve which starts in the stronger concentrations, attains its height in the intermediate zone and then declines. The maximum precipitation of the blue or violet is usually in dilutions of 1:160 to1 :640.

The flowing curves are the more frequent types encountered: 111221000 and 0123222100.

Colloidal Benzoin Reaction. Guillain, Lechelle and Laroche[57] have examined the spinal fluid in 19 cases of tuberculous meningitis, by colloidal benzoin. They found that a reaction occurred in the meningitic zone, starting in tubes 6 or 7 and being prolonged more or less far into tubes 12 or 13, less often into tubes 14 or 15. In some cases the reaction was limited to three tubes; occasionally a slightly different type of reaction was encountered in that there were two phases to the curve, one a rise in the syphilitic zone, then a fall to normal and a subsequent rise in the meningitic zone. In our series of 16 fluids these findings were corroborated, but in some instances reactions were obtained in which reduction was limited to only three tubes in the meningitic zone.[55]

Bacteriology of the Fluid. The percentage of cases in which the tubercle bacillus can be found in the spinal fluid differs according to the reports of various investigators. Some particularly fortunate and patient workers have been able to find the organism in the smear in 90 per cent to 100 per cent of their fluids. Others could locate the organisms in less than 50 per cent of the fluids. In the present collected group the tubercle bacillus was present in 73 per cent of the fluids. It seems to the writer that success depends on these factors: First of all, thorough search must be made in a number of smears, and, secondly, preparatory to this search the fluid must be treated in a certain manner: (1) Inasmuch as the reticulum is apt to be rich in bacilli, it is best to allow one test tube to remain in repose for twelve hours in the ice box in order to allow a good network to form. This is then carefully removed, spread out as thinly as possible on a slide and stained. (2) Another tube with fluid should be centrifuged for a prolonged

period, at least three hours, and a careful search then made in several smears of the sediment. (3) If these methods are not successful, some of the fluid, carefully collected so as to be free

TABLE XXXVII

QUANTITATIVE PROTEIN, SUGAR AND CHLORIDES IN TUBERCULOUS MENINGITIS (IN GRAMS PER LITER)

	No. of spinal fluids	Min.	Max.	Aver.
Protein	34	0.40	8.80	2.64
Sugar	33	0.10	0.50	0.27
Chlorides	31	5.00	6.87	6.25

TABLE XXXVIII

QUALITATIVE ALBUMIN, GLOBULIN AND SUGAR TESTS IN TUBERCULOUS MENINGITIS

	No. of spinal fluids giving various degrees of reaction					Total no. tested
	Negative	1+	2+	3+	4+	
Albumin	....	23 (17 per cent)	70 (51 per cent)	36 (26 per cent)	7 (5 per cent)	136
Globulin	....	33 (20 per cent)	76 (46 per cent)	38 (23 per cent)	16 (9 per cent)	163
Sugar (Fehling)	60 (39 per cent)	51 (33 per cent)	24 (15 per cent)	18 (11 per cent)	....	153

TABLE XXXIX

CELL COUNT IN TUBERCULOUS MENINGITIS

Total number of cell counts	131
Minimum count	0 cells per cu. mm.
Maximum count	1000 cells per cu. mm.
Average count	112 cells per cu. mm.

DIFFERENTIAL COUNT

Minimum percentage of lymphocytes	20 per cent
Average percentage of lymphocytes	76 per cent

RELATIVE DEGREE OF CELL INCREASE

Under 10 cells per cu. mm.	7 per cent of cell counts
Under 50 cells per cu. mm.	48 per cent of cell counts
Under 100 cells per cu. mm.	68 per cent of cell counts
Under 200 cells per cu. mm.	85 per cent of cell counts
Under 300 cells per cu. mm.	94 per cent of cell counts

of contamination, is submitted to the enrichment methods of Trembur by placing it in the incubator for from twenty-four hours to several days, before it is examined. (4) A new method devised by Cheer may also be utilized for this research. This test is performed as follows: 5 c.c. of spinal fluid are placed in a clean centrifuged tube, to which is added one-third to one-half its volume of 95 per cent alcohol. During the addition of the alcohol the tube is gently shaken all the time so as to distribute evenly its contents and to form a cloud of coagulum. If no coagulum forms, a drop or two of dilute egg albumin solution may be added. The tube is then centrifuged for one-half hour, or longer, in case the precipitate is scanty, and the supernatant fluid is carefully decanted, leaving the albuminous precipitate, which is removed by a capillary pipette to three or four slides and stained.

Biochemical Properties. Agglutinins are present. Complement appears to be absent (Froin[58]). Precipitins for tuberculin have been found to exist in the liquid (Vincent and Combe[59]). Toxicity has been noted at times (Sicard,[60] Armand-Delille,[61] Ramond, etc.).

Intrathecal Inoculation of Tuberculin. Kasahara[62] has recently described in 5 cases a method for diagnosis by means of the intrathecal injection of Koch's old tuberculin in doses of .01 to .002 gm. diluted in 1 c.c. of normal saline solution, after removing the usual amount of spinal fluid. A positive reaction is shown in twelve hours, the fluid showing a marked increase in lymphocytes and also of polymorphonuclear leucocytes, with the appearance of a large number of red cells and a pronounced augmentation of the protein. This test was applied to one of the cases in the present series. It would seem to be warranted only in cases in which further verification of the diagnosis seems desirable, or which it may possibly be employed as a therapeutic measure.

Post-Diphtheritic Paralysis

Few reports have been made on the subject of the cerebrospinal fluid in post-diphtheritic paralysis, and for this reason the characteristic findings are not by any means established. Many of the observations have been made by French investigators. The present study was based on the examination of 50 cerebrospinal fluids.[63]

Macroscopical Appearance. The fluid is clear, watery and limpid, without any ground-glass appearance and forming no fibrin web on standing.

Pressure. Few definite measurements are available, but these would indicate a tension of 15 to 40 cm. by the manometer of Claude. Roughly judging by the rate of flow from the needle and the amount of fluid obtained, the pressure is either normal or slightly or moderately augmented.

Protein. The protein content of the fluid in this series has usually been normal, but a certain minor proportion of cases (about one-third) has shown qualitatively an increase in albumin and globulin, the reaction being limited to a one-plus or a two-plus result. Only occasionally has a three-plus reaction been encountered.

Quantitatively the albumin has varied from 0.22 to 0.30 gm. per liter in the vast majority of cases.

Sugar. The reduction by Fehling's solution in post-diphtheritic paralysis has given qualitatively a good normal three-plus reaction in all the fluids examined. The few quantitative determinations by Lavergne, in 6 cases, have shown an increased content of sugar, with values of 0.64 gm. to 1.08 gms. per liter.

Cytology. In general and with only occasional exceptions, which possibly occur at certain periods of the disease, the cell count is within normal limits, ranging from 2 to 10 cells per cubic millimeter. Therefore, one of the common formulae in this disease is an "albumino-cytologic dissociation."

There are a few recent case reports in which a slight increase in cells was observed, ranging from 10 to 35 per cubic millimeter. Such cases, however, must still be regarded as more the exception than the rule.

Chlorides. One case in the literature gives a value of 6.9 gms. per liter (Ducamp and Carrieu[64]). In 12 fluids included in the present study the determinations[55] ranged from 7.1 to 7.9 gms. per liter.

Meningeal Permeability. There are no observations in the literature. In the cases of post-diphtheritic paralysis with local involvement only,[55] the permeability was under 10 mgms. per liter; while in the generalized paralysis a slight permeability (15 to 20 mgms. per liter) was at times encountered in the present series.

Colloidal Gold Reaction. No observations were found in the literature. The few spinal fluids examined by colloidal gold (about thirty in all)[63] showed a reduction in the high and medium concentrations, ranging from dilutions of 1:10 to 1:320 and expressed numerically with an average curve of 1122210000. As the paralytic

symptoms improve or are recovered from entirely, the reduction disappears.

Colloidal Benzoin Reaction. The 14 fluids included[55] in the present study indicate that the benzoin reaction is negative in the local forms of post-diphtheritic paralysis and that a reaction in the meningitic zone may be observed in the generalized forms.

Bordet-Wassermann Reaction. In the 30 cases in which the fluid was examined for the specific complement fixation test it was negative.

Toxin and Antitoxin. The work of Römheld,[65] of Guillain and Laroche[66] and later of de Lavergne and Zoeller[67] appears to show that toxin and antitoxin are not found in the cerebrospinal fluid in any appreciable quantities.

The Cerebrospinal Fluid in the Acute Infectious Diseases

1. Scarlet Fever. Dopter has seen 7 cases with cytological reaction, in 5 of which the increase was moderate. Dufour, Geroux, Hutinel,[68] Paisseau and Milhit have observed the same reaction. Gouget and Bernard have noted a polymorphonuclear leucocytic reaction. Tremolières and Caussade[69] state that the spinal fluid is clear, but at times may be hemorrhagic in the eruptive stage, with an augmentation of the albumin and urea values in cases with scarlatinal nephritis. They have also encountered, at times, a moderate lymphocytosis.

Our present study comprised twenty-two spinal fluids from 20 cases of scarlet fever, taken at various intervals after the onset, from the second to the twenty-second day of the disease, the majority being under ten days.

Macroscopical Appearance. All of the fluids were clear and colorless.

Pressure. There was almost uniformly a slight to moderate increase in the cerebrospinal fluid pressure.

Chemistry and Cytology. A slight increase in cells and albumin and globulin was noted in 5 cases, while a moderate increase was present in 2 instances.

The highest cell count cited was 30 per cubic millimeter, which was noted in 2 cases.

Fehling's reaction showed a normal three-plus reduction in all of the cases in which the examination was made.

Colloidal Gold Curve. This test was performed in 4 spinal fluids; it was negative in 2 instances and presented a very weak luetic (almost negative) curve in the remaining 2 cases.

2. Measles. In one case Mestrezat[11] observed that the fluid was clear but under increased tension. The chloride determinations gave a value of 7.23 mgms. per liter and the sugar content was normal; while in another patient Lemierre, Michaux and Limasset[70] detected an increased cytological reaction. Dopter, and Hutinel[68] had previously observed the same phenomenon.

Our present tabulation comprises nineteen spinal fluids from 18 patients, removed at intervals varying from the second to the seventeenth day of the disease, the majority being under seven days.

Macroscopical Appearance. All of the fluids were clear and colorless.

Tension. The pressure was indicated as slight or moderate, 15 to 30 c.c. being usually obtained.

Cytology. The cell count was normal in 9, slightly increased in 4 and was moderately increased in 5 cases (40 cells per cubic millimeter were noted in one patient). From 90 to 98 per cent of the cells were mononuclear leucocytes.

Chemistry. The albumin and globulin were normal in 15, one-plus in 3 and two-plus in 1 case. Quantitative albumin estimations in two fluids showed 0.22 gm. per liter.

Fehling's Reaction. This test showed a normal three-plus reaction in all of the fluids tested.

Colloidal Benzoin Reaction. This test was negative in the 2 cases so tested, four fluids in all.

3. German Measles. This present study included one case. The fluid was clear, under slightly increased pressure. The albumin and globulin were one-plus, Fehling's reaction was three-plus and the Wassermann was negative.

4. Epidemic Parotitis. Meningeal symptoms are not rare in mumps, but the variation in their intensity is very great indeed. It is impossible to classify these cases in regard to the type of meningeal reaction which they represent until we have more knowledge of the actual causative agent of the disease. In a number of the cases a true bacterial meningitis seems indicated by the intensity of the meningeal phenomena. The spinal fluid findings vary from a slight to a marked increase in lymphocytes up to several thousand cells per cubic millimeter, the fluid accordingly

being either clear or opalescent and the protein also slightly or markedly increased. The chlorides are apparently normal (Nobécourt and Voisin[13]).

5. Varicella. This series included 2 cases. The fluid was clear but under moderately increased tension in both. The cytology and chemistry were negative.

6. Variola. A few examinations are recorded in the literature. The freezing point seems to vary between $-52°$c. and $-72°$c. (Achard, Loeper and Laubry,[71] Thaon,[72] etc.). The chloride value is normal, while the sugar content is augmented, being as high as 1 gram per liter (Dircksen[41]).

7. Diphtheria. Comba[8] has examined the fluid in 4 cases of diphtheria and found that it was normal for albumin (0.14 to 0.20 gm. per liter) and showed quantitatively a normal sugar content (0.50 to 0.59 gm.). Crisafi[73] noted that the chloride content was 8.01 gms. per liter.

In this series there were 5 cases of pharyngeal diphtheria, including five fluids specified as having been withdrawn on the fifth or sixth day in 3 instances.

Macroscopical Appearance. All of the fluids were clear and colorless.

Tension. There was slight or moderate increase in the tension.

Cytology. A normal cell count was found in 3 patients and a slight increase in 2 instances.

Chemistry. Normal albumin and globulin values were reported in 1 case, one-plus in 3 cases and two-plus in 1 case. Fehling's test showed a normal reduction in all instances.

8. Diphtheria and Measles. In one case a clear fluid was obtained, showing a slight increase in cells of the mononuclear type, with a negative albumin and globulin reaction and a three-plus Fehling's reduction.

9. Pertussis. The specific gravity of the spinal fluid in pertussis is 1.007 (Ley[40]), the albumin has ranged from 0.16 to 0.20 gm. per liter in 6 cases (Comba), the sugar has been slightly augmented, from 0.60 to 0.80 gm. in 4 cases (Sicard and Langwelt[48]), and the total nitrogen has been found equivalent to 0.137 gm. per liter in 6 cases (Comba[8]).

The present study consisted of twenty-seven fluids from 26 patients, varying from the second to the eighteenth day.

Macroscopical Appearance. All of the fluids were clear and colorless.

Tension. There was a slight to moderate increase in pressure, from 15 to 20 c.c. being obtained in the majority of the cases. In one instance 75 c.c. are mentioned as being withdrawn (high tension).

Cytology. The cells were normal in 14, slightly increased in 5, moderately increased in 4 and greatly increased in 2 cases. One cell count of 75 per cubic millimeter was mentioned.

Chemistry. The albumin and globulin were normal in 12, while a one-plus reaction in 8, a two-plus in 3 and a three-plus in 4 cases were recorded.

Fehling's Reaction. There was a normal three-plus reaction in all.

Colloidal Gold Curve. This test was mentioned in 5 cases, being negative in 3 and showing a very low reaction in the luetic zone in 2 instances.

Bordet-Wassermann Test. This test was negative (2 cases).

10. Influenza (Including Grippe). In the present series there were twenty fluids from an equal number of patients.

Macroscopical Appearance. All of the fluids were clear and colorless.

Tension. An increased tension was present in a majority of the cases.

Cytology. This was normal in 12, slightly increased in 3 and moderately increased in 1 case (42 cells per cubic millimeter).

Chemistry. The albumin and globulin content was mentioned, in 11 patients, as normal in 8 and one-plus in 3 instances.

Fehling's Reaction. This showed a three-plus reaction in all of the fluids so tested.

Colloidal Gold Reaction. This test was mentioned in one case as negative.

Wassermann Test. This test was specified as negative in 6 cases.

11. Erysipelas. Nobécourt and Voisin[13] give the chloride content as normal.

The present tabulations include six fluids removed from the second to the twelfth day of the disease.

Macroscopical Appearance. The fluid was clear in all instances.

Tension. There was a slightly increased pressure, an average of 15 to 40 c.c. being removed.

Cell Count. This was normal in 4 and slightly increased in 2 cases (80 per cent mononuclear leucocytes).

Chemistry. The albumin and globulin were normal in 3, and one-plus in 3 instances.

Sugar. The sugar content was normal in all cases.

Bordet-Wassermann Test. This test was negative (2 cases).

12. LOBAR AND BRONCHOPNEUMONIA. The reaction of the spinal fluid to these acute pulmonary conditions depends on whether there are any meningeal symptoms present, and on the intensity of these symptoms.

Class 1. In most pneumonia patients, distinct meningeal symptoms are lacking, and the few punctures performed in this condition have apparently shown a fluid normal in chemistry and in cytological reaction.

Class 2. It is not uncommon, however, to encounter a definite meningeal syndrome of an amicrobic nature, in which the fluid is clear and presents a variable cytological and chemical reaction. The abnormal fluid shows only a slightly pathological variation. For detailed discussion of Class 2, see below.

Class 3. A third class of cases, relatively infrequent but similar in symptomatology, presents a spinal fluid in which the cells and chemistry and sugar are not greatly altered, but in which microorganisms (especially pneumococci) are found—attenuated meningitis.

Class 4. The fourth class of cases is represented by the frank acute bacterial meningitis, usually of pneumococcic origin, mentioned on page 325.

Pneumonia with Amicrobic Meningeal Syndrome (Class 2). In the present series there were 51 spinal fluids. The density was 1.006–1.008 (Comba[8]), and the freezing point $-51°$c. (Voisin[74]). The albumin was 0.15 to 0.30 gm. per liter, the chloride average was 6.08 gms. per liter in 32 cases, and the sugar was slightly augmented, 0.84 gm. per liter (Comba,[8] Mestrezat,[11] Voisin). The tension was increased, but the cytology of the cerebrospinal fluid was normal.

Macroscopical Appearance. All of the fluids were clear and colorless.

Tension. Increased pressure was present in nearly all of the cases, usually 15 to 25 c.c. being obtained.

Cytology. The cells were normal in 28, slightly increased in 10, moderately increased in 9 and greatly increased in 1 instance, the increased cell counts being 12, 12, 20, 27, 30 and 50 per cubic millimeter. The cells were almost exclusively mononuclear (90

TABLE XL

FLUIDS FROM DIVERSE ACUTE AND CHRONIC INFECTIONS

No. of case	Diseases	Macroscopical appearance of fluid	Amount, c.c.	Albumin	Globulin	Fehling's	Cell count	Special tests
1	Acute tonsillitis	clear	...	...	...	3+	7	
2	Acute tonsillitis	clear	...	...	...	3+	0	
3	Acute tonsillitis	clear	...	neg.	1+	3+	3	
4	Acute tonsillitis	clear	...	neg.	neg.	3+	normal	
5	Septic sore throat	clear	20	neg.	neg.	3+	45 per cent mononuclears	
6	Retropharyngeal abscess	clear	40	neg.	neg.	3+	slightly increased	
7	Retropharyngeal abscess	clear	10	neg.	neg.	3+	slightly increased	Sugar 0.68 gm.
8	Retropharyngeal abscess	clear	25	1+	1+	3+	25	
9	Acute pharyngitis	clear	..	...	neg.	3+	0	
10	Acute pharyngitis	clear	...	...	neg.	3+	3	
11	Acute pharyngitis	clear	...	...	neg.	3+	0	
12	Acute rhinitis	clear	...	1+	neg.	3+	0	
13	Acute bronchitis	clear	...	1+	3+	3+	5	
	Acute bronchitis	clear	...	neg.	3+	2+		
14	Acute bronchitis	clear	15	neg.	1+	3+	normal	
15	Acute bronchitis	clear	30	neg.	neg.	3+	5	
16	Acute bronchitis	clear	20	1+	1+	3+	20	
17	Sinusitis	clear	...	...	...	...	2	
18	Adenitis	clear	20	neg.	neg.	3+	normal	
19	Acute otitis media	clear	...	...	neg.	3+	0	
20	Acute otitis media	clear	...	...	neg.	3+	3	
21	Acute otitis media	clear	...	...	neg.	3+	29	
22	Acute otitis media	clear	...	...	neg.	3+	4	
23	Acute otitis media	clear	...	neg.	neg.	3+	2	
24	Otitis media	clear	15	neg.	neg.	3+	normal	
25	Otitis media	clear	35	neg.	neg.	3+	normal	
26	Otitis media	clear	100	neg.	neg.	3+		
27	Otitis media	clear	10	...	...	3+	moderately increased; 98 per cent mononuclears	
28	Otitis media	clear	25	2+	2+	3+	moderately increased; 90 per cent mononuclears	
29	Otitis media	clear	50	2+	2+	3+	moderately increased	
30	Otitis media	clear	8	neg.	neg.	3+	moderately increased	
31	Mastoiditis	clear	...	1+	1+	...	280; 94 per cent leucocytes	CGC 1176400000
32	Mastoiditis	clear	...	2+	2+	3+	32; 64 per cent polynuclears	
33	Mastoiditis	clear	...	neg.	neg.	3+	slight increase of mononuclears	
34	Mastoiditis	clear	25	neg.	neg.	3+	10	

35	Mastoiditis	clear	30	1+	1+	3+	40; 75 per cent mononuclears	
36	Mastoiditis	clear	...	neg.	neg.	3+	slight increase of mononuclears	
37	Mastoiditis	clear	20	2+	2+	3+	40	
38	Mastoiditis	clear	22	1+	1+	3+	11	
39	Mastoiditis	clear	15	neg.	neg.	3+	slight increase; 95 per cent mononuclears	
40	Orbital abscess	clear	50	1+	neg.	3+	normal	
41	Lung abscess	clear	...	...	neg.	3+	6	
42	Lung abscess	clear	...	neg.	neg.	3+	1	
43	Liver abscess	yellow	50	2+	1+	3+	normal	
44	Liver abscess	clear	...	neg.	neg.	3+	normal	CGC 0027543111
45	Abscess of chest	clear	25	1+	1+	3+	normal	
46	Empyema	clear	15	3+	3+	3+	slight increase; 80 per cent mononuclears	
47	Carbuncle of neck	clear	...	neg.	neg.	3+	2	CGC neg.
48	Carbuncle of neck	clear	...	...	neg.	3+	....	CGC neg.
49	Ulcer of foot	clear	12	...	neg.	3+	5	CGC neg.
50	Ulcer of the duodenum	clear	...	...	neg.	3+	5	CGC neg.
51	Chronic appendicitis, pneumonia	clear	...	...	neg.	3+	....	CGC 1122000000
52	Acute pyelitis	clear	...	1+	1+	3+	71 leucocytes	
53	Acute pyelitis	clear	...	1+	1+	3+	normal	
54	Acute pyelitis	clear	...	1+	1+	3+	9	
55	Acute pyelitis	clear	...	neg.	neg.	3+	normal	
56	Acute cholecystitis	clear	...	neg.	neg.	3+	2	
57	Acute cholecystitis	clear	...	1+	1+	3+	16	
58	Multiple arthritis	clear	...	1+	1+	3+	10	
59	Chronic arthritis, acute otitis media	clear	...	neg.	neg.	3+	1	CGC 0012210000
60	Osteomyelitis	clear	45	1+	1+	3+	0	
61	Osteomyelitis	clear	...	neg.	neg.	3+	4	
62	Osteomyelitis	clear	...	neg.	neg.	3+	0	
63	Chronic osteitis	clear	10	1+	1+	3+	4	
64	Chronic periostitis	clear	...	...	1+	...	6	
65	Septicemia with meningitis	clear	...	neg.	neg.	3+	75	
66	Septicemia, staphylococcus	clear	...	neg.	neg.	3+	2	
67	Septicemia, staphylococcus	clear	30	neg.	1+	3+	57; 90 per cent polynuclears	
68	Septicemia	clear	40	neg.	neg.	3+		
69	Septicemia	clear	25	neg.	neg.	3+	normal	
70	Septicemia	clear	8	neg.	neg.	3		
71	Septicemia	clear	25	neg.	neg.	3	15	
72	Septicemia	clear	10	2	2	3	moderately increased; 50 per cent polymorphonuclears	
73	Septicemia	clear	40	2	2	3	great increase; 98 per cent mononuclears	
74	Septicemia	clear	40	1	1	3	30	Sugar 0.30 gm.
75	Septicemia	clear	...	neg.	neg.	3	53	
76	Peritonitis	clear	15	neg.	neg.	3	slight increase; 95 per cent mononuclears	
77	Chronic otitis and brain abscess	clear	...	neg.	neg.	3	3	CGC negative
78	Acute follicular tonsillitis; acute nephritis	clear	...	...	neg.	3	7	
79	Scarlet fever, measles and septicemia	clear	...	...	...	...	....	CGC negative

per cent or more). In 2 cases there was a high mixed formula, 40 per cent and 55 per cent, polymorphonuclear in character.

Colloidal Gold Curve. This was practically negative in the two fluids examined, being limited to a very weak reaction in the first four or five tubes of one case (luetic zone).

Quantitative Chemistry. In grams per liter this was as follows: total nitrogen, 0.0967, and 0.2272 gm.; urea, 0.0535 gm. and 0.10 gm.; non-protein nitrogen, 0.2228 gm., and sugar, 0.923 gm.

13. Typhus Fever. An amicrobic meningeal syndrome in the course of exanthematic typhus fever is not uncommon. Fontecilla and Sepulveda have encountered a number of cases of such toxi-infectious origin, which have generally recovered completely. They found the spinal fluid non-toxic for laboratory animals. An increased amount of cerebrospinal fluid was constantly noted, 20 to 40 c.c. being removed. Often the first puncture was bloody and the subsequent fluids were xanthochromic. The chlorides were diminished (6.0 gms. per liter), the glucose normal, the albumin augmented (0.30 to 2.0 gms. per liter) and the leucocytes normal or very slightly increased (15 cells per cubic millimeter). The reaction of Felix Weil was always precociously positive. Matthes[75] has encountered a cloudy liquid and Eskuchen[76] a case with intense leucocytosis and considerable albumin.

In the present tabulations there were 6 fluids, all clear and under increased tension. The cell count was increased in all cases. This increase was slight in 2 cases, moderate in 2 (40 to 67 lymphocytes per cubic millimeter) and great in 2 instances (over 100 lymphocytes). The albumin and globulin were normal in 1 and increased in 5 patients; in 2 patients the reaction was two-plus. The sugar content was normal.

14. Typhoid Fever. The meningeal symptoms encountered in typhoid fever afford by their degree of intensity an index to the severity of the case. Clinically the reactions vary, and the spinal fluid findings range from those of a purely negative character to those of an acute bacterial meningitis. This latter is considered in speaking of the various other forms of acute purulent meningitis. In this instance are considered the amicrobic meningeal syndromes.

The literature gives briefly the following data: density, 1.007 to 1.011 (Comba[8]); albumin, 0.12 to 1 gm. per liter; chlorides, 6.6 (Crisafi[74]) to 7.8 gms. per liter (Mestrezat[11]); sugar, 0.51 to 0.53 gm. per liter (Sicard), and non-protein nitrogen, 0.134 to

0.154 gm. per liter (Comba[3]). The specific agglutinins are not found in the cerebrospinal fluid unless a true typhoid meningitis exists (Widal and Sicard), or some affection which causes increased meningeal permeability. No cytological reactions were mentioned. In the present series there were 17 spinal fluids.

Macroscopical Appearance. All of the fluids were clear and limpid.

Tension. This was slightly to moderately increased. The amount removed was 5 to 30 c.c.

Cytology. This was mentioned in 14 cases as normal in 7, slightly increased in 6 and moderately increased in 1 case, the cell counts ranging from 0 to 23 cells per cubic millimeter.

Chemistry. The values were normal in 7, slightly increased (one-plus) in 6, and two-plus in 1 case.

Sugar. Fehling's reaction was normal in all.

Quantitative Nitrogen. The total nitrogen was 0.157 gm. and the non-protein nitrogen, 0.136 gm. per liter (1 case).

Colloidal Gold. This test was mentioned in 2 cases, presenting a luetic curve extending somewhat into the meningitic zone in one, and negative in the other case.

Discussion

The following questions submitted to Dr. Regan before the Commission, together with the answers to them, are here reported verbatim.

Dr. Dana: Do the majority of these diseases that you report occur in children?

Dr. Regan: The vast majority of the fluids mentioned were obtained from children, but not all of them.

Dr. Dana: Your description of meningitis takes me back about forty years, when I remember reading a very careful description of meningitis in Ziemsen's "Encyclopedia of Medicine." So many forms were described that I never could understand which was which; so when I undertook to write my book, I reduced the forms of meningitis to about two, and both I and the students have found this number to be quite satisfactory.

It seems to me that you have gone back to the times of Ziemsen in specifying so many kinds of meningitis, dependent upon the kind of bacteria, etc., and whether there are bacteria or not. I do not think this is really necessary. A student should understand that meningitis is sometimes due to toxins and sometimes to bacteria; he should know the general symptoms of the disease, learn the cause by a lumbar puncture, but he does not need to have a different name for every causal condition.

Dr. Regan: Simplicity, I think, has some very good points about it. That was one reason why I presented this classification, to indicate the complicated

method of looking at this subject. The types of meningitis may be viewed according to the simple method of which Dr. Dana has mentioned the advantages. It seems to me that original contributions to our knowledge along this line will be facilitated by the proper classification of these conditions.

Dr. Patterson: How frequently does Dr. Regan find acetone present in the spinal fluid and what significance does he attribute to its occurrence? What method does he use for determining meningeal permeability?

Dr. Regan: We have ourselves performed very little work on the detection of acetone in the spinal fluid until lately, and there has been very little mention made of this determination in the literature of the acute meningeal syndromes.

In regard to the meningeal permeability test, there are two tests employed, the iodide and the nitrate. In the former, 2 to 5 grams of potassium iodide are administered during several days and then the spinal fluid is tested for this substance. In the nitrate test 1 gram of sodium nitrate is given for every kilogram of body weight and the lumbar puncture is performed three hours later.

Dr. Strauss: In Dr. Regan's use of the term "Meningism," he employs the word to indicate a clinical entity, does he not?

Dr. Regan: It is, of course, always secondary, but it is used in a way as an entity; that is, for the purpose of formulating a distinct idea of what meningism really is.

Dr. Strauss: But is not the term "meningitis" really applicable to a syndrome, which can occur in any condition where there is an irritation of the meninges? Even a tumor may give us meningism. Is it not possibly a bad use of the term, to try to use it as an entity; would it not lead to confusion?

Dr. Regan: In using the term "serous meningitis" in this way I have only been following the precedent of many authoritis in that particular phase of the subject.

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Chapter XXII

THE HUMAN CEREBROSPINAL FLUID IN SYSTEMIC AND DIFFUSE DEGENERATIVE DISEASES INVOLVING THE NERVOUS SYSTEM

CLARENCE A. PATTEN, M.D.

THERE are very few of the systemic and diffuse degenerative diseases in which careful and consistent studies of the spinal fluid have been undertaken. For the most part, reports in the literature cover isolated cases and one always questions their reliability, since other physical factors may not have been considered. The only evidence admissible upon which conclusions may be based comes from those who have made a group study of some special condition and reported all the findings from both clinical and laboratory standpoints. From such materials, one is reasonably safe in tabulating statistics.

Multiple Sclerosis

Few other conditions, conscientiously investigated thus far, have revealed the marked cerebrospinal fluid findings that are reported in multiple sclerosis. Ayer and Foster[1] reported the findings in 38 verified cases in 1921. They found no pressure alterations beyond the normal. The cell counts in forty-eight specimens of fluid showed 0 to 5 cells in 61.2 per cent, 6 to 10 cells in 16.7 per cent, 11 to 20 cells in 4.2 per cent and 42 cells in 2 per cent.

The total protein showed an increase in 50 per cent of the cases; the globulin reaction was negative in 22 cases and positive in 9. The Wassermann was negative throughout. The gold chloride test gave more definite findings than any other estimation. Forty-two readings were made, showing a "paretic" type of curve in twenty-one fluids (16 patients), a "luetic" type in seven fluids (7 patients), positive reactions in three fluids (3 patients) and negative reactions in eleven fluids (10 patients). This shows that the "paretic" curve was obtained in one-half the number of fluids examined and nearly one-half of the number of cases.

The sugar averaged .048 per cent in fourteen fluids. The non-protein nitrogen averaged 21.5 mgms. in eleven determinations. The average in eleven determinations of chloride content was 688 mgms. per 100 c.c. No acetone bodies were found. The creatinine averaged 1.78 mgms. per 100 c.c., and urea 15.5 mgms. per 100 c.c.

Eskuchen[2] found 3 out of 4 cases to have entirely negative fluids; the fourth case showed a pleocytosis, increase of globulin and a paretic gold curve. Jaeger and Goldstein[3] reported in a few cases a "slight colloidal gold reaction, there being a faint color change in the first 4 to 5 tubes." Flesch[4] reported 8 cases showing a completely negative fluid in one case, a slightly positive colloidal gold curve with other tests negative in one case, and a paretic gold curve in the remaining 6 cases. Kaplan and McClelland[5] reported 2 cases in which one had a negative and the other a paretic gold curve. Later, Kaplan[6] reported 18 cases in which only one had the paretic type of curve. Oetiker[7] found globulin increased in one case with other findings negative, and one case with no pleocytosis or globulin but with a partial reduction in the colloidal gold reaction.

Rotstadt[8] stated that in 75 per cent of cases there is no cellular increase in multiple sclerosis. Moore[9] stated: "Together with the clinical evidence, it is believed that the spinal fluid picture is fairly constant and that, other things being equal, such a picture is a strong argument in favor of a diagnosis of multiple sclerosis. In its absence, the diagnosis becomes at least doubtful." Eskuchen,[10] at a later date (1919), reported that multiple sclerosis in a large percentage of cases showed typical tabetic or paretic colloidal gold curves. Sicard[11] found 2 cases with a pleocytosis and 5 cases without it. Eskuchen,[12] again, stated that the spinal fluid findings varied, 50 per cent showing a normal fluid. In 30 per cent of cases, the pressure was slightly increased, the globulin weakly positive, the cell count 20 to 30 and the gold reaction of the "luetic" type. The cerebrospinal fluid Wassermann was negative. In about 20 per cent of cases the pressure was definitely increased, the globulin moderately positive, the cell count 30 to 50, the spinal fluid Wassermann negative and the gold curve of the "paretic" type. Boyd[13] examined the fluids in 18 cases, finding the fluids clear, the pressure normal, the cells varying from a slight to a moderate lymphocytosis, but never exceeding 30 and the globulin slightly increased. On the other hand, Mestrezat[14] found three

fluids negative in every respect. Tucker,[15] in 4 cases of multiple sclerosis, noted that the pressure varied in each case, that cells numbered not more than 5 and the gold curve was of the paretic type in only one case.

A review of selected hospital case records[21] with serological studies and typical clinical syndromes, shows that for the most part the current literature is in agreement. It is regrettable that necropsy confirmation is not obtainable in the majority of instances. However, basing conclusions on the material at hand, there were found: normal appearance and pressures of fluids, not infrequent cellular increases, occasional increases in globulin content and gold sol curves ranging from negative, atypical and luetic to paretic types. The paretic types occurred in less than one-third of all cases. Ayer and Foster[1] mention the variation in types of curves in the stationary and progressive cases, finding the paretic type most commonly in the latter. To this observation, there might be added the age factor, for in 6 cases, personally observed, where definite clinical symptoms were present, the indefinite or negative curves were found in patients between fifteen and thirty years of age, while the paretic curves were the rule in the thirty to forty-five year period. This naturally raises the question of the time of onset of the disease: whether it might not originate at a much younger age period than we are led to believe by the usual histories.

The figures for the sugar content have varied remarkably and show no uniformity. The same is true of the protein constituents of the fluid. These two substances have no apparent relationship to the colloidal gold reaction. In a few cases in which the chlorides were estimated, they were found high, usually over 600 mgms. per 100 c.c.

Epilepsy

Mestrezat[14] stated that the majority of cerebrospinal fluids are normal in idiopathic epilepsy. There may be a slight increase in albumin and sugar. Lochelongue[18] reported the fluids to be normal in epilepsy and the cell count within normal limits.

Eskuchen[12] noted that in the majority of cases of idiopathic epilepsy the fluid was unchanged, except that the pressure was elevated during an attack. He stated that the globulin may be increased and that there is seldom a pleocytosis.

Levinson[16] made the same observations concerning the increase in the pressure during an attack. He also believes there is an increase in the amount of fluid during an attack but that there may or may not be an increase in the intervals.

Donath[19] found choline in crystals and by chemical tests in 18 out of 21 cases of idiopathic epilepsy. This observation has not been corroborated by others, the investigation apparently not having been undertaken.

One hundred hospital case records and statistics compiled by Tucker showed the following results: (1) Fluid always clear; (2) pressures (reported in 36 cases) normal to slightly increased; (3) cells consistently within normal limits; (4) globulin negative to slightly increased; (5) Wassermann reaction negative (those showing a positive reaction were excluded); (6) the gold solution curve negative or showing a slight reduction (in nine fluids).

Amyotrophic Lateral Sclerosis

Mestrezat[14] studied the fluids in two cases of amyotrophic lateral sclerosis and in one case found the albumin and chloride content normal, but the sugar content very much increased. In the other case there was a slight hyperalbuminosis and a mild leucocytosis. Eskuchen[12] found a mildly positive globulin reaction, and the other constituents normal.

Our hospital case records[21] show no changes of any character, so far as the ordinary routine examinations of the spinal fluid are recorded. No apparently independent and thorough investigations have been carried out in this disease.

Syringomyelia

In one case of syringomyelia studied by Mestrezat[14] an increase in albumin and sugar was found, all other findings being normal. Eskuchen[12] and Sicard[11] recorded all findings normal. Boyd,[13] quoting Kaplan, stated that there may be a marked protein increase without a pleocytosis. He mentioned one case with a xanthochromia. In 4 other cases the fluids were normal.

In several hospital case records,[21] the fluids were found clear, cells normal, globulin absent except in one case, sugar content slightly increased in 33 per cent and the celloidal gold solution negative.

Cerebral Tumors

Lochelongue[18] stated that in cerebral tumors, the fluid pressure was usually increased, the albumin content normal, the sugar increased, at times a moderate lymphocytosis and the chloride values normal or nearly so. Boyd[13] reported that the pressure was sometimes enormously increased, and usually definitely increased. The cell count, as a rule, was normal but might be increased. The protein content, as a rule, was not increased, but more likely to be so if the tumor was a gumma. Rehm is reported by Boyd as recording the presence of cholesterin crystals and fat in a cholesteatoma of the base of the skull. Boyd found cholesterin ester crystals in a tumor of the optic chiasm.

Alpers[20] reported a study of 102 ventricular fluids in cases of tumor of the brain, with particular reference to the Lange gold test. In his cases, the cells were increased in nine instances; between 7 and 20 in seven fluids, 73 in one fluid and 375 in one fluid. The quantitative albumin was increased in thirty-seven fluids, the total proteins increased in forty-five fluids, and the colloidal gold solution reduced in thirty-five fluids. The gold solution curve, however, was not uniform and reductions did not take place at all frequently in the so-called "tumor zone." He stated that most of the cases showed a reduction in the luetic or tabetic zones.

Huntington's Chorea

Eskuchen reported no characteristic changes.[12]

Our hospital records[21] confirm Eskuchen's report.

Paralysis Agitans

Eskuchen[12] reports no characteristic changes in this disease. Our hospital case records,[21] however, have shown that there is a gold solution reaction in a majority of cases. In 10 case reports, there was reduction in seven fluids. In all but one of these the reduction occurred in the middle tubes (0001121000); it was slight in most instances, but moderate in two fluids (0233453210). In every other respect the fluids resembled those found in arteriosclerosis.

Subacute Combined Degeneration

Boyd[13] examined two fluids in this condition and reported that the globulin was slightly increased. The cells and other constituents

were normal. In Boyd's report Kaplan is quoted by a description of 3 cases with a marked globulin increase and no pleocytosis.

A study of hospital case reports[21] shows a clear fluid, normal pressure and cellular content, globulin absent or slightly increased in a few cases (2.3 per cent), sugar quite variable, Wassermann reaction negative, and the colloidal gold curve negative in 98.5 per cent. Those fluids showing a gold solution curve gave no uniform reduction.

Spastic Spinal Paralysis

This disease is not, strictly speaking, a clinical entity, but usually a part of some process in which spasticity is a predominating feature. It should show, therefore, in so far as cerebrospinal fluid determinations are concerned, a reaction consistent with the underlying condition. Eskuchen stated that the fluid is for the most part normal, although there are often a mild pleocytosis and a mildly positive globulin reaction. No pleocytosis was found in any of the hospital case records reviewed.

Spinal Muscular Atrophy

Eskuchen[12] found an increase in pressure of the spinal fluid, but otherwise no uniform changes. Mestrezat mentioned a similar result.

Arteriovascular Disease

In generalized cerebral arteriosclerosis without focal disease the fluid is practically unchanged, according to Eskuchen.[12] There may be a slightly positive globulin reaction and a mild pleocytosis. With encephalomalacia, pleocytosis and a globulin increase are frequently encountered.

A study of many hospital case records[21] reveals a distinct difference in the fluid findings of uncomplicated cerebral arteriosclerosis and hemorrhage, thrombosis and embolism. In arteriosclerosis there were found no changes in pressure, color, number of cells, sugar content or colloidal gold reactions. In hemorrhage, the cellular elements were naturally increased in many cases because of the presence of blood, but in those cases in which the fluid was clear, about 33 per cent showed a moderate pleocytosis, with the majority of cells of the lymphocytic type. Occasionally large mononuclear leucocytes were found and rarely a small number of polymorphonuclear leucocytes. In one-half of the cases, the

sugar was definitely, though not markedly, increased. Other findings were normal. In embolism and thrombosis, the sugar content was mainly affected. Here high percentages were found. Alpers, Campbell and Prentiss[17] have reported similar observations.

Degenerative Conditions

A number of congenital and degenerative diseases and birth injuries are grouped under this heading. These include the mental deficiencies, Little's disease, cerebral diplegia, dystonia musculorum deformans, tuberous sclerosis, Friedreich's ataxia, amaurotic family idiocy, spina bifida, Thomsen's disease, Alzheimer's disease, progressive spinal muscular atrophy, bulbar paralysis and hydrocephalus.

Eskuchen[12] found no definite spinal fluid change in bulbar paralysis, in Alzheimer's disease, in mental deficiency or in Little's disease. In the latter condition Eskuchen quotes Holzman as finding increased pressure in one case and Plaut, Rehm and Schottmüller as finding a lymphocytosis. In one hospital case[21] both increased pressure and a pleocytosis were found, but the other findings were negative.

In 23 case records on hydrocephalus, the fluid changes are not typical in any way. The fluids were clear in all but one instance, the cells were increased in 6 cases, but the globulin reaction was negative in 9, doubtful in 5 and increased in 8 cases. The sugar content was increased in 13 cases and not reported in 2. The Wassermann reaction was negative in all cases in which it was reported (50 per cent). The colloidal gold curve is given in 8 cases, being negative in 4, showing a mild reduction in the first 5 to 6 tubes in 3 cases and a stronger reduction in the last 5 tubes in one case.

Friedreich's ataxia, dystonia musculorum deformans, tuberous sclerosis and Thomsen's disease showed normal findings throughout.

One case of spina bifida had 26 cells, but other findings were negative.

The birth injury cases showed a pleocytosis and increased sugar percentages, but otherwise normal findings.

V Amaurotic idiocy (one case) showed a very slight increase in cells and a luetic curve.

Discussion

The following question submitted to Dr. Patten before the Commission, together with the answer to it, is here reported verbatim.

Dr. Jelliffe: Has Dr. Patten any information on the cerebrospinal fluid findings in amyotrophic lateral sclerosis?

Dr. Patten: Mestrezat states that in 2 cases of amyotrophic lateral sclerosis which he studied, he found the albumin and chloride content to be normal but the sugar content very much increased in one; in the other case there was a slight hyperalbuminosis and a mild leucocytosis. Eskuchen found a mildly positive globulin reaction, but all the other constituents were normal. Those are the only cases that I have from the literature. From the hospital records, no case has been found showing changes of any character, so far as the ordinary routine examinations are concerned. This brings up the same point alluded to before, that in a great many of these conditions sufficiently careful chemical and other studies have not been made of the spinal fluid. Outside of those two reports from the literature, there has apparently been no independent effort made to study amyotrophic lateral sclerosis.

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Chapter XXIII

THE EFFECT OF ORGANIC BRAIN AND SPINAL CORD CHANGES ON THE SUBARACHNOID SPACE, CHORIOID PLEXUS AND THE CEREBROSPINAL FLUID*

GEORGE B. HASSIN, M.D.

LESIONS of the central nervous system afford excellent opportunities for study of the numerous problems pertaining to the origin, nature, circulation and mode of escape of the cerebrospinal fluid. While some facts obtained from histopathological studies correspond, others seem to be at variance with experimental findings. Especially is this true of the mode of origin of the cerebrospinal fluid, the function of the chorioid plexus and the significance of the subarachnoid space and the cerebral ventricles.

According to prevalent views the cerebrospinal fluid originates in the lateral ventricles from the chorioid plexus. Some (Studnicka,[1] Kafka[2]) maintain that the ependymal cells of the ventricles and the spinal canal, as well as other formations (the paraphysis and the epiphysis), also participate in its production. Some (Weed,[3] Weigeldt[4]), again, hold that the perivascular channels of Virchow-Robin are contributory agents in the elaboration of this fluid, while a smaller group of workers (Schmorl,[5] Lewandowsky,[6] Askanazy,[7] Spina,[8] Tilman,[9] Bungardt,[10] Becht,[11] Klestadt[12]) asserts that the cerebrospinal fluid has nothing to do with the function of the chorioid plexus, being, according to the majority, a product of the brain tissue.

In favor of each of the foregoing opinions a great number of experimental and purely anatomical facts are presented. Histopathological data are practically lacking. However, representing as they do changes produced by Nature herself, histopathological phenomena obviously are of great interest and importance. Reviewed elsewhere by the author,[13] they pertain chiefly to the changes exhibited by the subarachnoid space in every lesion of

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the brain or the spinal cord. In this contribution, additional facts are adduced tending to show that the cerebrospinal fluid is probably a product of the tissue fluids of the central nervous system and that, like the villi of the arachnoid, the chorioid plexus is not an organ of secretion, but of excretion or absorption of some contents of this body fluid.

The Effect of Organic Brain and Spinal Cord Changes on the Subarachnoid Space

It is definitely established, especially by the work of Weed,[14] that the tissue fluids in the brain, "contained within the perineuronal, pericapillary and perivascular systems are poured into the subarachnoid space." By injecting the latter, in the lumbar region, under a moderately high pressure, with an isotonic solution of equal parts of potassium ferrocyanide and iron-ammonium citrate and subsequently immersing the animal's head in formaldehyde containing a one per cent solution of hydrochloric acid, Weed produced precipitation of Prussian blue granules in the subarachnoid space, the Pacchionian bodies, the cervical lymph glands and along the sheaths of some cranial nerves (olfactory, trifacial, hypoglossal). No granules were found in the brain tissue itself. Figure 49 shows the subarachnoid space injected not with Prussian blue, but with carcinoma cells. These cells reached the cerebral spaces through the lymph glands of the neck from a primary carcinoma of the breast. The carcinoma cells thus traveled to the meningeal spaces practically along the pathway followed by the Prussian blue granules in Weed's experiments, and, as in the latter, infiltrated the subarachnoid spaces without invading the cerebral tissues.

Another section showed that the Pacchionian bodies also were invaded by carcinoma cells. This fact again corresponds with the experimental findings (Key and Retzius, Weed) that the contents of the subarachnoid space have a tendency to flow away from the brain toward the Pacchionian bodies, the principal organs of their elimination.

A similar phenomenon is illustrated in Figure 50, from a case of cerebrospinal meningitis. The subarachnoid space is packed with pus which, in the form of a broad band, is separated from the parenchyma of the cerebellum by a thick layer of plasma cells. As in the cases of meningeal carcinoma, neither plasma cells nor

pus was found in the cerebellar parenchyma. Were the flow of the fluid *from* the subarachnoid space *to* the brain, as suggested by some (Mott[15]), the brain tissues would have been invaded by the same pathological elements that crowded the surrounding spaces. However, this may be the case if the latter are excessively infiltrated. For instance, injecting the subarachnoid space of animals,

Fig. 49. Meningeal carcinoma. The subarachnoid space is infiltrated with carcinoma cells. The veins of the pial prolongations (*Y*) and the brain substance (*Br*) itself are free from carcinoma cells. *Ar*, arachnoid membrane; *Sub*, subarachnoid space; *P*, pia; *A*, artery; *V*, a large thrombosed vein. Toluidin blue × 80.

under high pressure, with a 2 per cent solution of potassium ferrocyanide and iron-ammonium citrate and subsequently rendering the brain anemic by cutting both carotids and jugulars, Weed[16] caused penetration of the mixture into the adventitial spaces of Virchow-Robin; that is, he reversed, as it were, the flow of the cerebrospinal fluid. The same fact is demonstrated by Figure 51.

It not only shows the subarachnoid space excessively infiltrated with carcinoma cells, but also the superficial capillaries and small blood vessels markedly invaded by the same cells which were scattered even beyond the blood vessel walls. A like invasion of the superficial vascular spaces obtains in cases of severe meningitis. Ranke[17] long ago pointed out that the phenomena of encephalitis, such as perivascular infiltrations, etc., are usually absent in

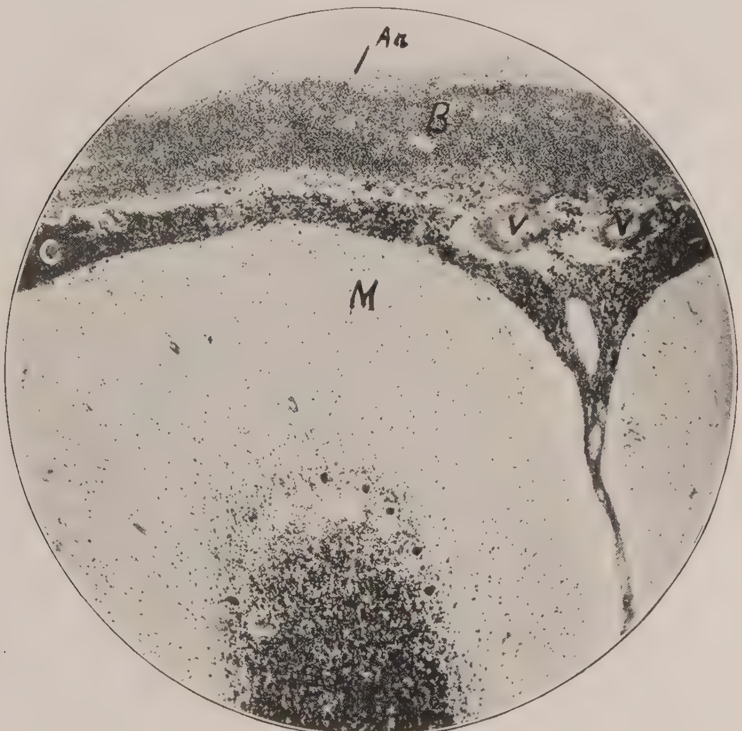

FIG. 50. Cerebrospinal meningitis. The subarachnoid space (*B*), packed with pus cells, is separated from the cerebellar parenchyma (*M*) by the pia (*C*) infiltrated with plasma cells. *Ar*, arachnoid membrane. *VV*, blood vessels of the pia, with infiltrated adventitia. Toluidin blue × 60.

tuberculous meningitis; if present, they are found only in the superficial layers of the brain.

The foregoing experimental and pathological facts demonstrate that a communication exists between the subarachnoid and the perivascular spaces and that the contents of the latter are not derived from, but most likely are discharged into the former,

thus largely contributing to their contents, the cerebrospinal fluid.

Pathological as well as experimental data seem to show that the discharge of the perivascular contents obtains also in the direction of the ventricles. In other words, the ventricular con-

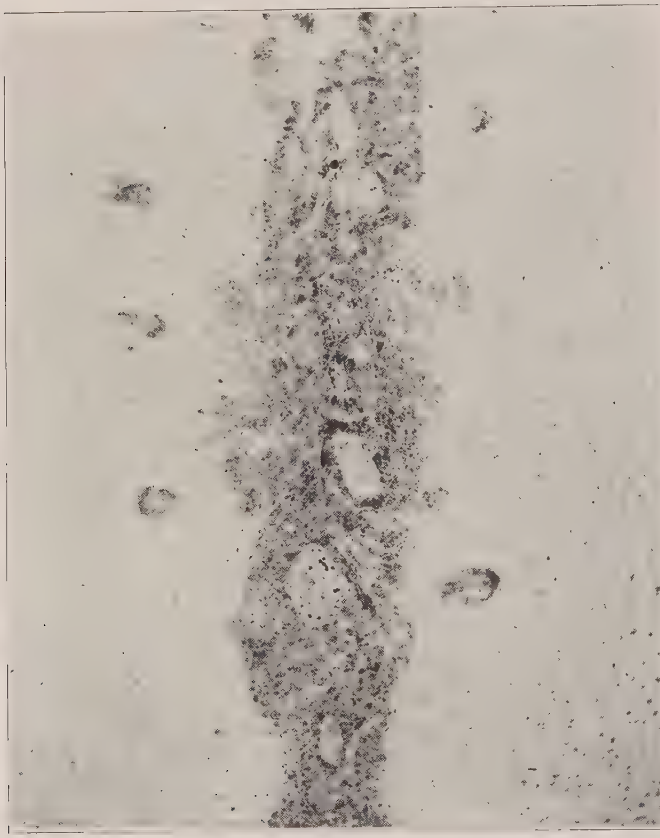

Fig. 51. Carcinomatous infiltration of the pia is associated with a similar infiltration of the superficial capillaries of the cortex. Toluidin blue × 60.

tents are probably also derived from the perivascular spaces of the cerebral blood vessels, being subsequently discharged into the subarachnoid space through the usual channels, the Sylvian aqueduct and the foramina of the fourth ventricle. Bruno,[18] after intradural injections of a solution of sodium ferrocyanide, found

neither the brain substance nor the ventricles colored. But after intracerebral injections of the same solution he demonstrated intense coloration of the pia, the base of the skull, the lateral and third ventricles and the Sylvian aqueduct. Bruno concluded that the fluid reaches the ventricles by way of "lymph spaces."

Forster[19] injected India ink into the cortex of rabbits. Six hours after an injection he found small India ink granules already in the

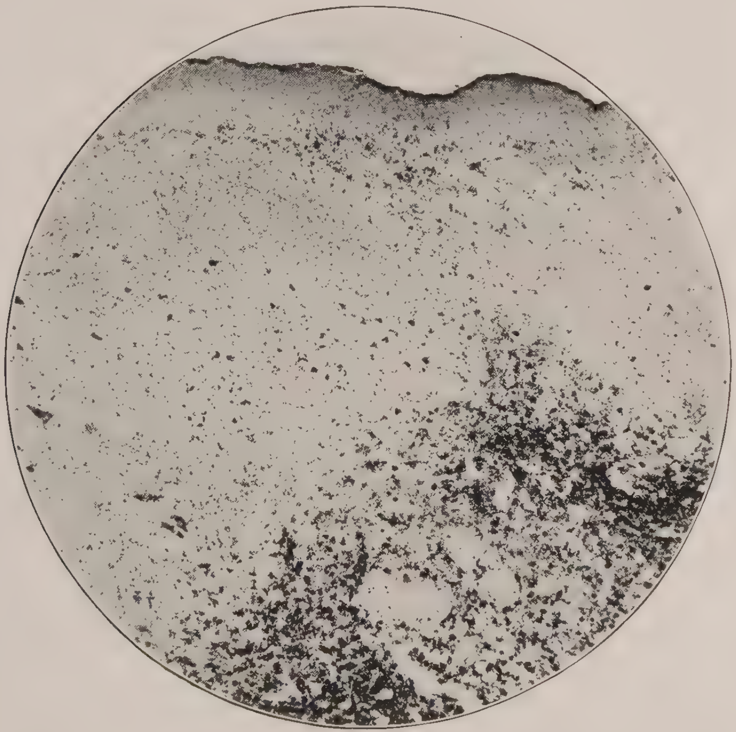

FIG. 52. The black masses are fat globules covering the area occupied by a degenerated twelfth nerve nucleus. The blood vessels are surrounded by fat enclosed within gitter cells; other pale areas in the darkened region are mostly blood vessels; the ependyma of the fourth ventricle is packed with fat. Herxheimer scarlet red hematoxylin stain × 60.

cells of the pia, in the lymphocytes and in the blood vessel walls. He came to the conclusion that the "lymph current is toward the cerebral surface," for otherwise the ink granules could not have reached the subarachnoid space.

Wislocki and Putnam,[20] injecting the lateral ventricles of hydrocephalic kittens and young rabbits with a solution of potassium ferrocyanide and iron-ammonium citrate or a 0.1 per cent solution of trypan blue, found the dyes in the lateral and third ventricles, Sylvian aqueduct, fourth ventricle and throughout the central canal of the spinal cord. The trypan blue granules were also found in large numbers in the cerebral perivascular spaces. These authors concluded "that fluid currents exist between the

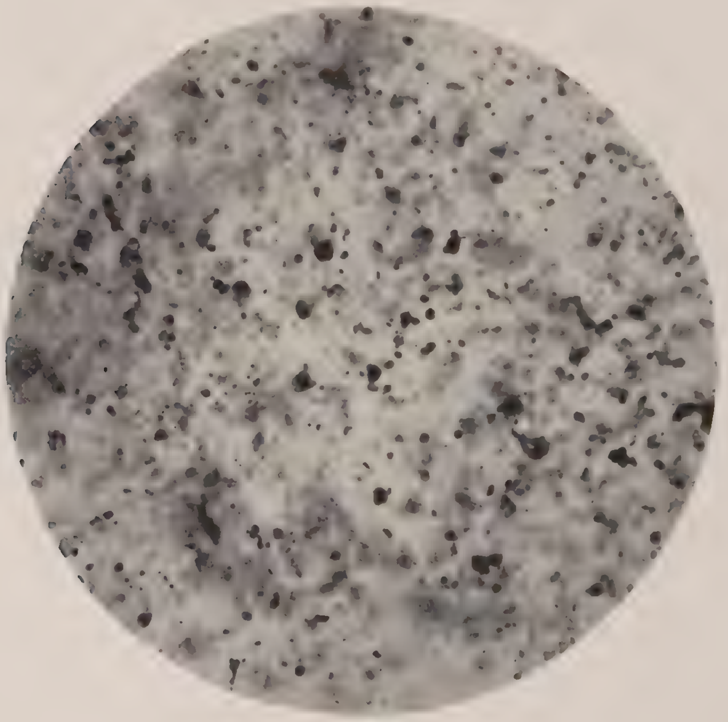

Fig. 53. The subarachnoid space of the case pictured in Figure 52 shows numerous fat globules and droplets. Herxheimer stain × 230.

dilated ventricles and the neighboring vessels under the abnormal conditions of a heightened intraventricular pressure."

Numerous histopathological facts confirm the experimental findings quoted, which seem to show that the contents of the subarachnoid space and the ventricles are derived from the central nervous substance. In Figure 52, for instance, is shown a large focus

of brain softening filled with lipoid material. This material, enclosed within gitter cells, was also present in large amounts in the perivascular and subarachnoid spaces (Fig. 53). In any other degenerative condition, as well as in vascular softening of the brain or spinal cord, lipoid material may be easily demonstrated within the dilated adventitial spaces of Virchow-Robin on its journey from the focus of the lesion to the subarachnoid space. Years ago Bruce

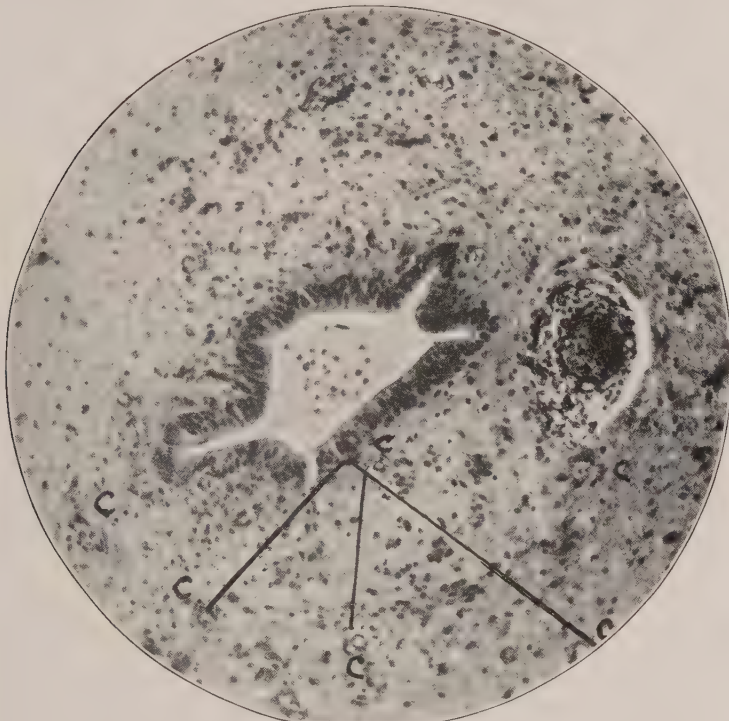

FIG. 54. Poliomyelitis; central canal of cord. The lumen shows granular material and numerous hematogenous elements among which polyblasts with pale curved nuclei predominate. These elements are similar to those present in the adjacent blood vessels (*C*, *C*, *C*).

and Dawson[21] called attention to the fact that in subacute cord degeneration the lipoid material tends to move toward the surface of the spinal cord, being carried along the perivascular lymph spaces. Bruce and Dawson assert that it lodges in the inner layer of the pia from which it probably moves toward the subarachnoid space, but not to the central canal or the gray matter.

However, some cases of acute poliomyelitis and malignant growths of the brain show that the contents of the perivascular spaces may be discharged into the central canal and the ventricles. In Figure 54 the Virchow-Robin spaces near the central canal are enormously infiltrated with hematogenous elements which are also present in the central canal. In a case of cerebral carcinoma (Fig. 55)

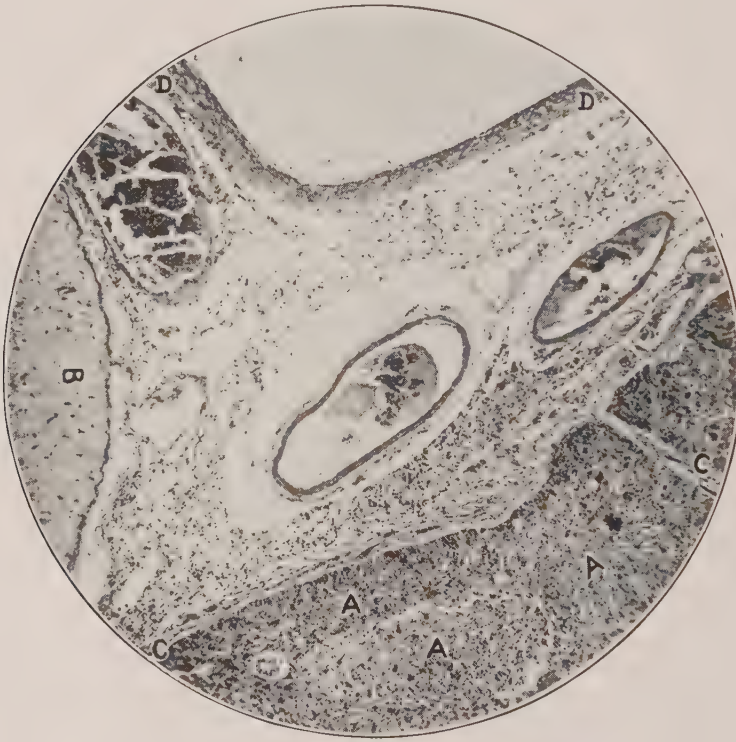

FIG. 55. Cerebral carcinoma. The piarachnoid is distended, the subarachnoid space packed with cell bodies. *A, A, A,* foci of carcinoma separated from the proliferated pia (*C, C*) which should be compared with the well formed pial covering of the brain at *B. D, D,* hyperplastic arachnoid. Van Gieson × 60.

the pia was markedly hyperplastic and infiltrated (lymphocytes, polyblasts, mesothelial cells and numerous other elements), while the lateral ventricles were invaded by a carcinomatous growth (Fig. 56).

Of especial interest are cases of so-called solitary tubercle of the spinal cord. As Figure 57 demonstrates, the parenchyma of the

spinal cord was transformed into a cheesy, necrotic mass separated from the subarachnoid space and the dura mater by a thickened and hyperplastic pia. The membranes were densely proliferated, possessing all the features of a tuberculous meningitis which is always present in cases of solitary tubercles of the spinal cord. This can be explained on the assumption that in the latter the tissue fluids carry the infectious material to the subarachnoid space

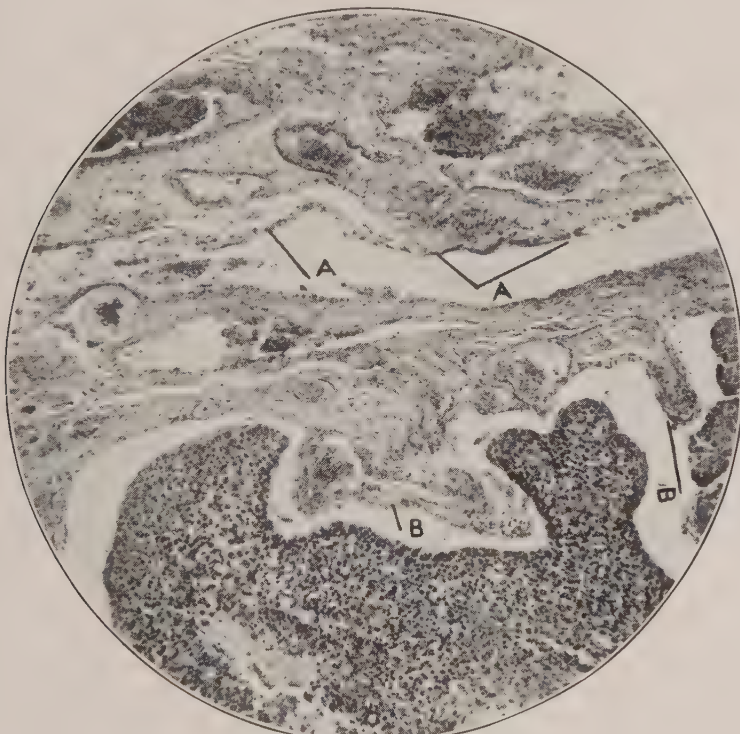

Fig. 56. Chorioid plexus invaded by carcinoma. *A*, *A*, epithelial tuft cells; *B*, *B*, tufts of the plexus, much resembling the villi of the arachnoid; the mass below is a carcinoma focus. Van Gieson × 80.

where it sets up a meningitis. If the material is of a malignant character, sarcoma, for instance, a diffuse sarcomatosis of the meninges will result. This evidently was so in Matzdorf's case[22]: a sarcoma of the dorsolumbar region which was associated with a diffuse sarcomatosis of the pia and dura mater. In Rindfleisch's case[23] "a sarcoma of the optic thalamus and chorioid plexus

invaded the pia mater by continuity" ("Flächenhaft") and in Westphal's[24] case a thalamic sarcoma involved the piarachnoid and the entire circumference of the spinal cord without invading the latter. It is rather peculiar, remarks Rindfleisch, that an extramedullary sarcoma usually spares the parenchyma, while

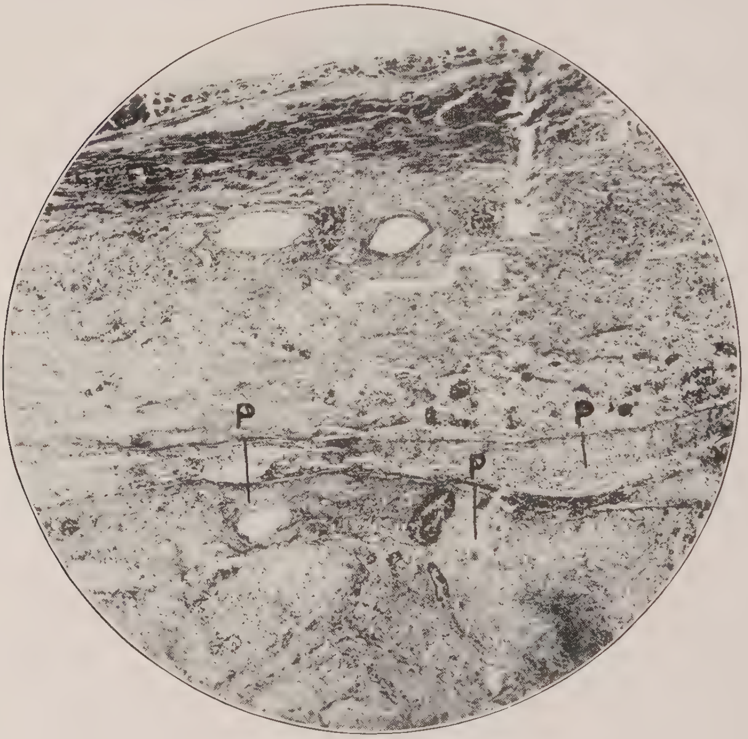

Fig. 57. Solitary tubercle of the spinal cord. The lower half of the photomicrograph representing the spinal cord, covered with tubercles, is divided from the upper half—the infiltrated and thickened dura—by a split and infiltrated pia (*P*, *P*, *P*). Bielschowsky stain × 60.

the favorite form of sarcomatosis of the central nervous system is a combination of nodules in the parenchyma with a diffuse sarcomatosis of the meninges.

In Figure 58 is illustrated the condition of the subarachnoid space in a case of an encapsulated abscess. It contains lymphocytes, gitter cells packed with lipoid material, macrophages enclosing

decomposed elements (lymphocytes, pigment granules, etc.), mesothelial cells, polyblasts and other elements.

In Figure 59 is pictured the subarachnoid space from a case of cerebral hemorrhage. Here are abundant pigment globules within various cell bodies, especially lymphocytes, mixed with macrophages, polyblasts and mesothelial cells. It must be pointed out that cases of cerebral hemorrhage are not altogether satisfactory for a study of the relationship between the perivascular and the subarachnoid spaces. Often it is not possible to determine

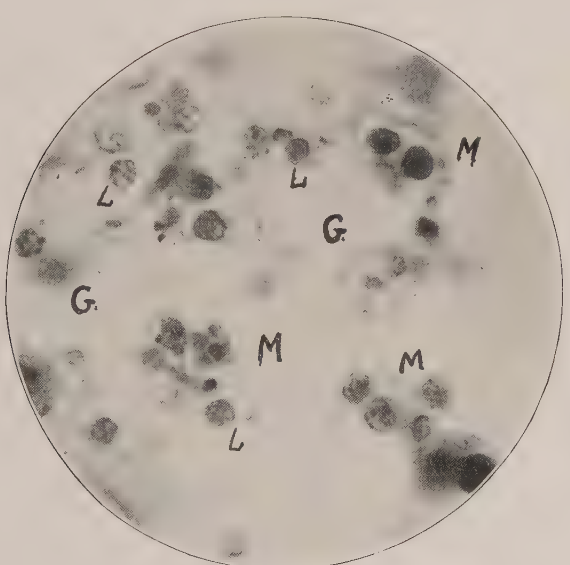

FIG. 58. The subarachnoid space of a case of an encapsulated brain abscess. *M* indicates macrophages; *G*, *G*, gitter cells; *L*, lymphocytes. Bielschowsky counterstained with Alzheimer-Mann × 1200.

the nature of the pigment granules in the piarachnoid, many such granules being so-called formol pigment, while in the perivascular spaces pigment granules sometimes cannot be found at all. This may be due to their rapid absorption or to other causes not yet known or little understood. However, the presence of the blood pigment in the subarachnoid space can be easily demonstrated chemically. Thus in a cerebral hemorrhage the spinal fluid may appear clear, yet give a positive benzidene test, provided, of course, the hemorrhage is not traumatic and is at least twenty-four

hours old. On the other hand, in softening of the brain or any other condition not associated with hemorrhage, the benzidene test in the spinal fluid is always negative.

That the spinal cord waste products are discharged into the subarachnoid space is vividly shown in Figure 60 from a case of myelomalacia. Here the spinal cord, in some areas, was transformed into a soft mass which consisted of myelophages and gitter

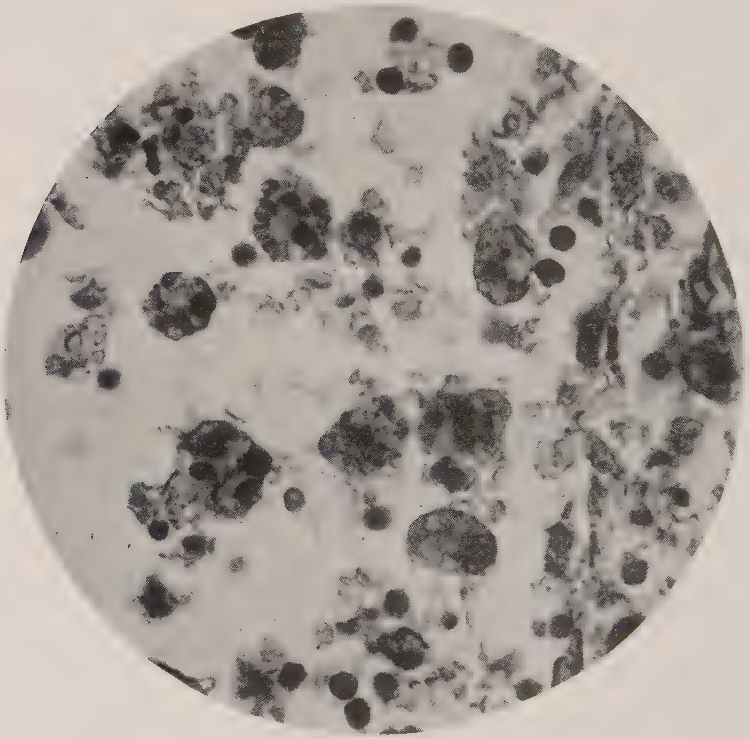

Fig. 59. The contents of the subarachnoid space in a case of capsular hemorrhage. It contains a large number of macrophages filled with blood pigment. Toluidin blue × 650.

cells. In spite of the fact that the pia was greatly proliferated and hyperplastic, the subarachnoid space contained a large number of gitter cells which evidently reached this space by way of the perivascular spaces.

In some pathological conditions no waste products, such as lipoid material, tubercle formations, decomposed blood pigment,

etc., can be demonstrated in the subarachnoid space, but they may show their presence by marked reactive phenomena on the part of the piarachnoid. This is illustrated in Figure 61 from a case of lead encephalitis. The pia is enormously proliferated, forming whorls that much resemble a connective tissue growth. This is

FIG. 60. Myelomalacia. The softened spinal cord (*Sp. C.*) is represented by gitter cells which are also abundant within the distended meshes of the pia (thick black strands). Bielschowsky stain $\times$ 400.

probably due to the action of the lead discharged by the tissue fluids of the brain into the subarachnoid space. In other cases, again, the reactive phenomena are much milder and appear merely as a proliferation of the mesothelial cells. This has been beautifully

demonstrated by Essick.[25] By injecting laked blood into the subarachnoid space of animals he followed up the various reactive phenomena in the mesothelial cells—their enlargement, transformation into macrophages, grouping into clusters, etc.

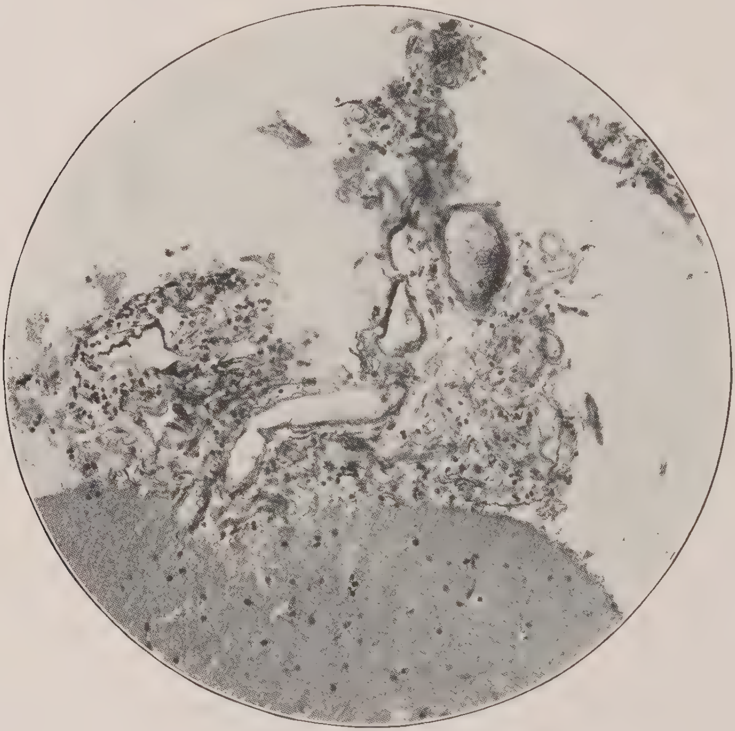

Fig. 61. Lead encephalitis. Hyperplasia of the pia. Combined Bielschowsky-Alzheimer-Mann stain × 150.

The Effect of Organic Brain and Spinal Cord Changes on the Chorioid Plexus

The subarachnoid space thus exhibits more or less definite changes that vary according to the condition of the parenchyma, their nature depending on that of the latter. The tissue fluids of the central nervous system, laden with waste products, are drained by the subarachnoid space and the ventricles for further elimination of the waste. In the former it occurs mainly through the action of the villi of the arachnoid (the Pacchionian bodies), in the latter through that of the villi (tufts) of the chorioid plexus. While such a function of the Pacchionian bodies is not disputed, that of the

chorioidal villi is rejected by the majority of workers, as pointed out, on purely experimental grounds. Experimental findings, however, are by no means conclusive; they are not uniformly interpreted and are not so convincing as the facts furnished by histopathological research. For instance, Figure 62 shows the chorioid plexus from a case of ventricular hemorrhage, the tuft cells containing large quantities of blood pigment absorbed from the hemorrhagic focus. The exact nature of the blood pigment

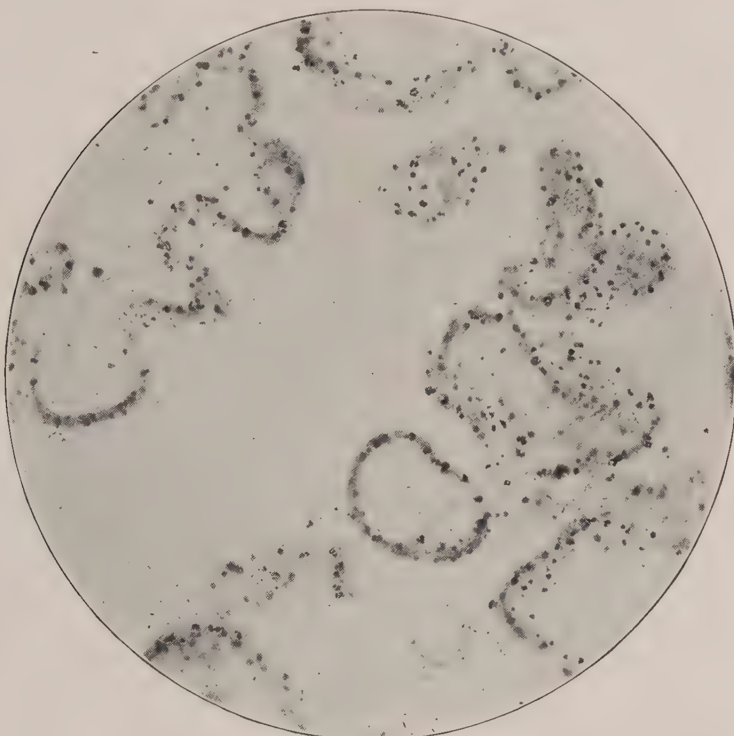

FIG. 62. Ventricular hemorrhage. The tuft cells of the chorioid plexus are covered with blood pigment granules. Unstained specimen × 230.

could not be determined, for this did not give the reaction for hemosiderin or any other known blood pigment. The granules probably consisted of broken-up hemoglobin. Similar findings were recorded by Askanazy, Wüllenweber[26] and the author (in a case of pontile hemorrhage[27]).

Much more striking seems to be the condition of the chorioid plexus in degenerative conditions of the brain. Here the tuft

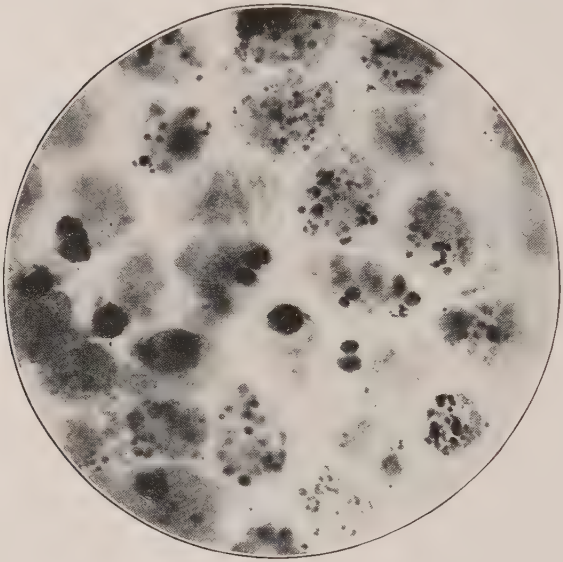

FIG. 63. The chorioid plexus from a case of superior and inferior polioencephalitis. The tuft cells are densely covered with lipoids. From a case reproduced in Fig. 52. Herxheimer stain × 1200.

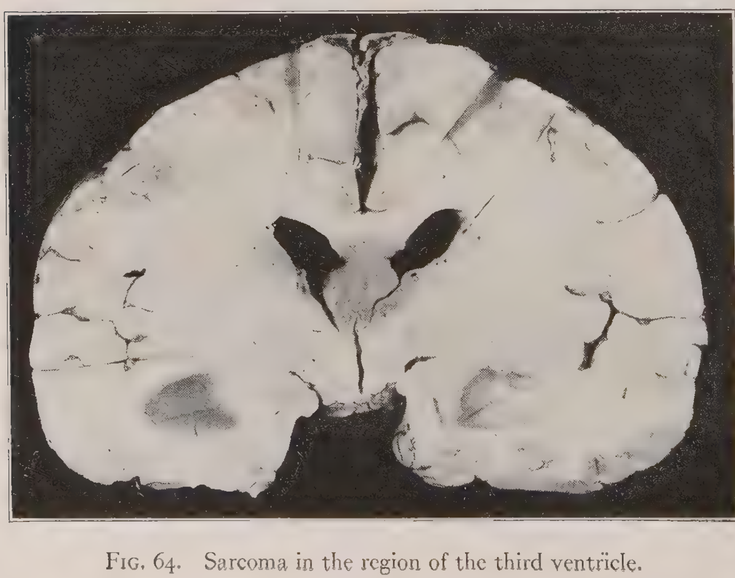

FIG. 64. Sarcoma in the region of the third ventricle.

cells are sometimes so densely covered with lipoid material that some are transformed into typical gitter cells (Fig. 63). In Figure 56, from a case of cerebral carcinoma already mentioned, is shown the invasion of the chorioid plexus stroma with carcinoma cells, the tuft cells themselves remaining intact.

These instances demonstrate that the tuft cells of the chorioid villi are capable of picking up some substances from the ventricular

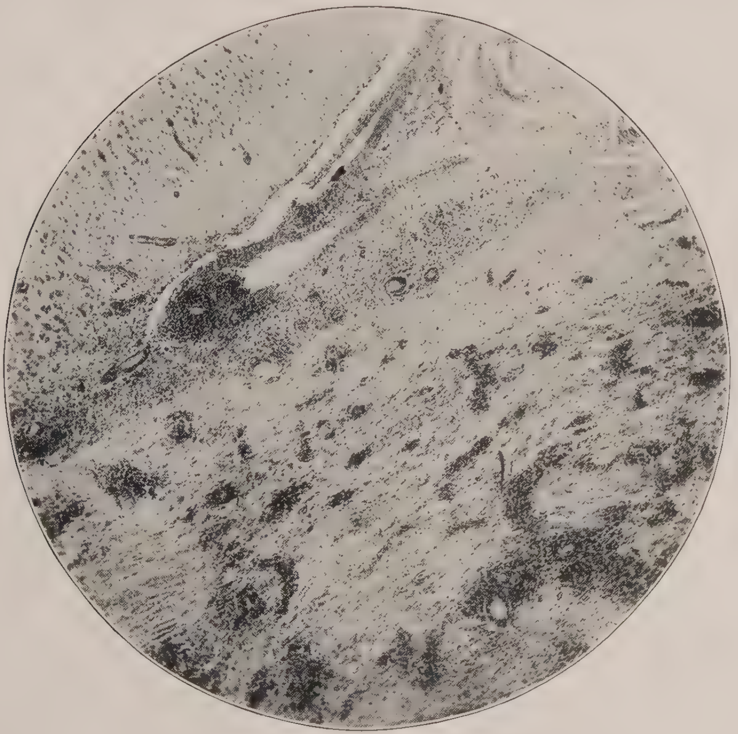

FIG. 65. Optic thalamus of the tumor case reproduced in Fig. 64. The pia is infiltrated with tumor cells; the brain substance, covered with blood vessels, is enormously infiltrated with sarcomatous cells. Toluidin blue × 36.

contents and of remaining indifferent to others, such as carcinoma cells or some dyes (in the experiments of Putnam and Wislocki, Goldman[28] and others).

The effects of parenchymatous changes on the subarachnoid spaces, ventricles and the chorioid plexus were most strikingly combined in a case of a tumor in the region of the third ventricle. The clinical picture resembled that of epidemic encephalitis. The

tumor (Fig. 64) occupied the area of both anterior pillars of the fornix and the septum pellucidum, and invaded the corpus callosum and the optic thalami. The temporal horns of the lateral ventricles were filled with a gelatinous mass clearly shown at the left in the illustration. The tumor, a sarcoma, was extremely cellular, and invaded the adventitial spaces of the adjacent blood vessels (Fig. 65). What is still more remarkable, the invading cells were found in large masses in the subependymal areas of Ammon's horn (Fig.

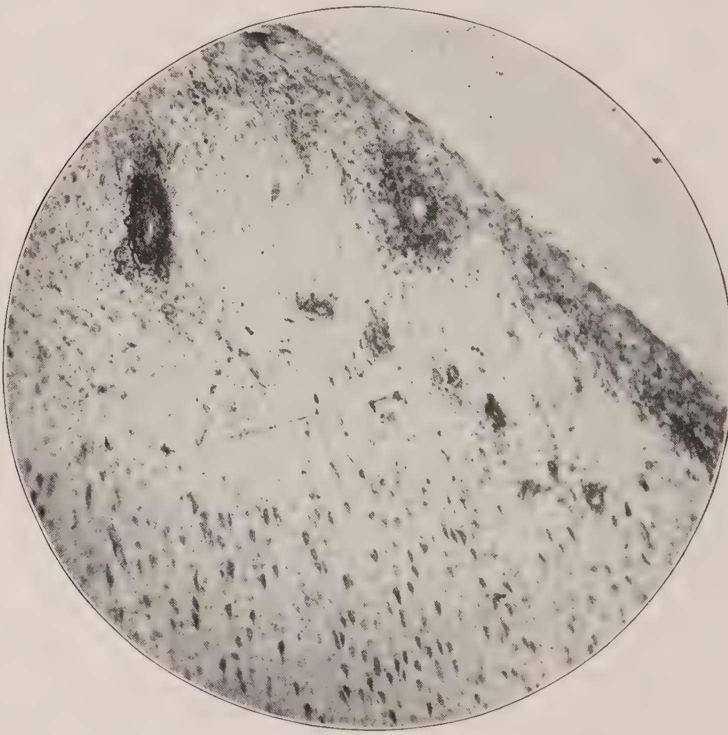

Fig. 66. Ammon's horn of the tumor case reproduced in Fig. 64. Marked infiltration of the blood vessels and capillaries with sarcomatous cells. Toluidin blue × 60.

66), the subarachnoid space and the chorioid plexus (Fig. 67). In the region of the caudate nucleus they were seen breaking through the ependyma and invading the lateral ventricles which were greatly dilated. The flow of the pathological cell bodies from the parenchyma of the brain through the perivascular spaces to the ventricles and chorioid plexus is thus most clearly depicted.

As to the gelatinous fluid, it was evidently the product not of the chorioid plexus but of the sarcoma and the discharge of the latter's catabolic products into the ventricles along the perivascular spaces. Whatever the explanation of the origin of the gelatinous fluid, this fluid in the present case denotes a lesion not of the chorioid plexus but of the brain substance itself. A similar fluid has been seen by the author in two other cases of severe parenchymatous brain lesion: one of a calcified tumor of the pituitary body and one of a case of torular meningoencephalitis.

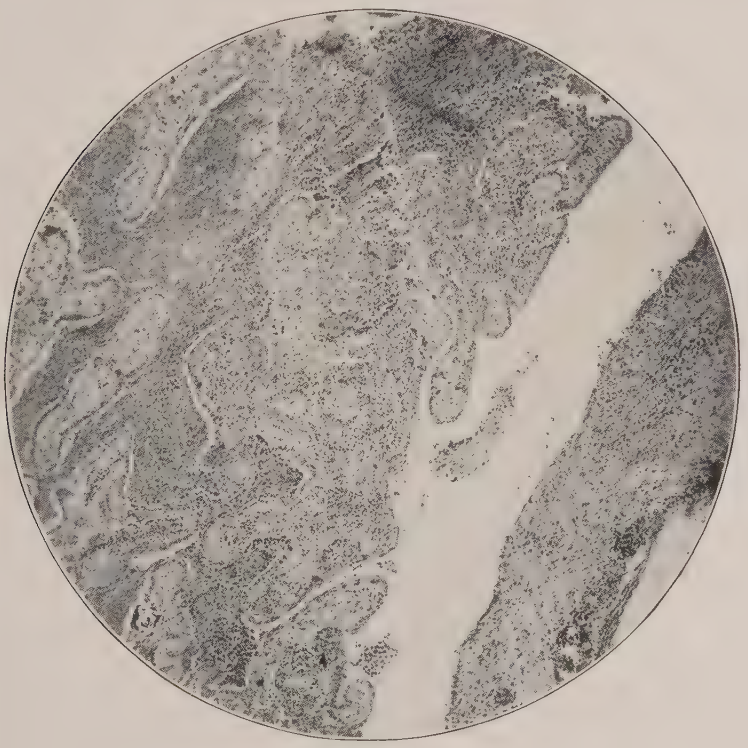

Fig. 67. The chorioid plexus of the lateral ventricles (sarcoma of the third ventricle). The stroma is markedly infiltrated with tumor cells. Toluidin blue × 20.

The Effect of Organic Brain and Spinal Cord Changes on the Cerebrospinal Fluid

The foregoing case, in my opinion, well illustrates the fact that the cerebrospinal fluid does originate in the brain tissues. Carrying the waste of the latter, the cerebrospinal fluid discharges it by

way of the perivascular channels into the ventricles and the subarachnoid space for final elimination by the villi of the arachnoid and of the chorioid plexus. Such a conception of the origin of the spinal fluid conveys an idea of a purposeful activity of this body fluid, whereas the secretion theory does not give an adequate explanation of its function. Nor can the secretion theory explain the morphological or chemical properties of the cerebrospinal fluid in various lesions of the central nervous system, such as general paralysis of the insane, brain syphilis, tabes, multiple sclerosis and similar conditions. Without going into a lengthy discussion, one may merely indicate that the catabolic products carried from a paretic brain to the ventricles and the subarachnoid space are of a different nature from those found in tabes or brain syphilis. Nor can the secretion theory give any explanation of the histopathological facts here recorded. The excretion or absorption theory, in contrast, not only explains them satisfactorily, but is supported by a number of experimental facts. The most remarkable fact is furnished by the famous work of Weed and his co-workers (McKibben,[29] Hughson[30]). It pertains to the behavior of the brain after injections of hypertonic or hypotonic solutions. The former produce a shrinkage of the brain, with a subsequent fall in the spinal fluid pressure; the hypotonic solutions (distilled water, for instance), cause an increase in the bulk of the brain, with an increased spinal fluid content as well as "an increase in the production of the cerebrospinal fluid." The increase in the size of the brain occurs quite rapidly and is due to an accumulation of tissue fluids in the interspaces and the perivascular lymph spaces. Even assuming that the increase in the bulk of the brain was gradual, during the entire time the experiment lasted (about one hour, 10 c.c. of distilled water being injected per minute), it is rather difficult to conceive how the chorioid plexus cells could produce, in one hour, such an enormous amount of fluid sufficient to fill up all the interstitial spaces and cause an enlargement in the bulk of the brain. Weed[31] tried to explain this by an increased activity of the chorioid plexus cells which, as he showed, become almost twice as large as the normal cell. Their distal border becomes rounded and bulging, the nucleus is displaced, but not altered in chromatin content or in size, the appearance of the tuft cell being on the whole quite similar to that of a cell "ruptured into a fluid environment." Though the chorioid plexus, in Weed's opinion, plays a great rôle in the formation of the fluid following injections of

hypotonic solutions, he admits that "the nervous system itself seems, on morphological grounds, to share in the process of new formation of the cerebrospinal fluid, the fluid being passed into dilated pericellular spaces and thence along the perivascular channels into the subarachnoid space."

An equally interesting physiological experiment is recorded by Foley[32] in collaboration with Percival Bailey. After intravenous injections of hypertonic salt solutions, the manometer, when inserted into the cisterna cerebellomedullaris and filled with a solution of potassium ferrocyanide and iron-ammonium citrate, showed a displacement of the solution into the subarachnoid space with subsequent precipitation of Prussian blue granules in the usual channels of absorption: the arachnoidal villi and the sheaths of the nerves. The granules, however, were also found in the perivascular spaces of the brain and the ventricles. The conclusion drawn was that the hypertonic solution, by increasing the osmotic value of the blood, induced absorption of the fluid from the perivascular spaces of the brain. This withdrawal of fluid from the perivascular spaces causes a retrograde passage of the cerebrospinal fluid from the subarachnoid space into the perivascular spaces and finally into the capillaries of the brain substance. Also there is, as Foley remarks, a retrograde passage of fluid from the subarachnoid space to the ventricular system where "reabsorption through the chorioid plexus occurs."

Conclusions

1. The secretion theory of the cerebrospinal fluid holds that this fluid is largely elaborated by the chorioid plexus.

2. The excretion or absorption theory, in contrast, holds that the fluid comes from the tissue fluids of the brain.

3. The secretion theory is mainly based on experimental and anatomical data, which may be equally well explained by the excretion theory.

4. The latter theory renders understandable the changes obtaining in the subarachnoid space and chorioid plexus in various brain and cord lesions.

5. As the secretion theory is powerless to explain the relationship between the brain and subarachnoid changes, it must be assumed that the cerebrospinal fluid is produced by the brain tissues themselves; the villi of the chorioid, like those of the arachnoid, being

organs not of secretion, but of excretion or absorption of the waste from the spinal fluid.

Discussion

The following questions submitted to Dr. Hassin before the Commission, together with the answers to them, are here reported verbatim.

Dr. Meyer: I should like to ask Dr. Hassin whether he has had any experience with the blocking of the circulatory pathways of the cerebrospinal fluid, either through inflammatory processes or by tumor or other material which might be suspended in the cerebrospinal fluid.

Dr. Hassin: No, I have had none.

Dr. Strauss: Mr. Chairman, I understood that Dr. Hassin stated in his opening remarks that he intended to show that the chorioid plexus had nothing to do with the formation of spinal fluid. I should like to ask him if my understanding of his statement is correct.

Dr. Hassin: Absolutely.

Dr. Strauss: Then I wish to go on record, as follows: all the evidence that we have collected from embryological, clinical and experimental studies has shown that, while it is probably not the only source, yet the chorioid plexus is the main source of the cerebrospinal fluid; that the question whether the chorioid plexus secretes or acts as a filter in the production of the cerebrospinal fluid is not as yet determined; that there is no question that the perivascular spaces empty into the subarachnoid space; and that the work that Dr. Hassin has presented is in confirmation of a fact that I think is rather generally accepted.

Dr. Hassin: Of course, I did not have the time to elaborate my findings, but before we accept the theory that the chorioid plexus secretes the spinal fluid, we must explain why this structure in one case contains excessive amounts of lipoids, in another instance, blood, and in other cases, again, why its stroma is filled with tumor cells. If we accept the absorption or, more correctly, the excretion theory of the chorioid plexus, the foregoing phenomena can be easily interpreted. But, as I said, I did not have time to explain every slide in detail; that is probably why I could not convince Dr. Strauss that the chorioid plexus serves as a filter for the tissue fluids which are poured from the brain into the ventricles and has absolutely nothing to do with the elaboration of the spinal fluid.

Dr. Globus: Dr. Hassin is, no doubt, familiar with the work of Weed, particularly with reference to the embryology and the histogenesis of the piarachnoid. He is, then, no doubt, familiar with the facts that the piarachnoid membrane did not at one time exist as two independent membranes in the embryo, and that a split occurred later in embryonal life, giving rise to the piarachnoid space. Weed also suggested that the piarachnoid space is in a way predestined to open up at a given critical moment—at a time when the intraventricular pressure due to the elaboration of the fluid by the chorioid plexus becomes so great as to cause a break in the pia, and in this way allow the fluid to escape into and spread in the piarachnoid space through its various channels and cisterns. Is this not a fairly good proof, on embryological ground,

that the chorioid plexus does secrete cerebrospinal fluid, whether as a selective secretion or by filtration?

It is found at times that the piarachnoid membrane fails to split, resulting in an internal or external hydrocephalus (Dandy), for there is a constant formation of cerebrospinal fluid with lack of an absorbing surface. Can this not be considered as further proof that the choroid plexus is responsible for the formation of the cerebrospinal fluid?

Dr. Hassin: As to the embryological phase of spinal fluid formation, I wish to state that I did not pursue studies along these lines. I have attempted to present histopathological proofs that the chorioid plexus does not produce the spinal fluid. I do not know how much brain substance there was in the pig embryos studied by Weed; and I do not know whether or not the spinal fluid came from the embryos' brains, in order to open up the meningeal spaces. I cannot understand that part of it at all. But I know another work of Weed which is more important. When he injected hypotonic solutions—distilled water—into the venous system of animals, he produced, in one hour, enormous enlargement of the brain. He admits himself that the enlargement of the brain was due to the increased production of the spinal fluid, and he also admits that the increased amount of the spinal fluid came from the perivascular and cerebral tissue spaces as well as from the hypertrophied cells of the chorioid plexus; the cells of the latter became doubled in size and height and produced an increased amount of the spinal fluid. I can not understand how the cells, even hypertrophied and with an excessive production of fluid, could cause an increase in the size of the brain within one hour. The explanation of this remarkable phenomenon might be this: By injecting hypotonic solutions, one increases the osmotic pressure, as a result of which the brain becomes overfilled with fluid which is poured through the perivascular spaces into the ventricles and the subarachnoid space; and the tuft cells, being too busy, as it were, to absorb or to filter excessive amounts of fluid, become increased in size. In my opinion, the work of Weed proves that the absorption or excretion theory of the chorioid plexus is more correct than the secretion theory.

Dr. Strauss: I should like to ask Dr. Hassin if he would therefore throw out of consideration entirely Weed's work upon the absorption of the spinal fluid largely, almost entirely (although he admits some absorption through the lymphatics), through the arachnoidal villi. That, I believe, has been the principal work that has been done regarding the absorption of the spinal fluid, and it proved rather conclusively that the channel of absorption was through the arachnoidal villi into the dural sinuses.

Dr. Hassin: No, I would not. The spinal fluid contents are absorbed by several channels, among these the arachnoidal villi and the chorioid plexus. Both act probably as mere filters for the cerebrospinal fluid, rendering it absorbable by other channels (the perineural spaces, for instance).

Dr. Meyer: I should like to ask Dr. Hassin whether he has any evidence of any special incrustations on the chorioid plexus in the process of absorption, where the fluid contains particles which would not be likely to be swallowed up by the ependyma.

Dr. Hassin: We find lipoid material over the tufts of the chorioid plexus when the ventricular fluid is filled with lipoids; when the ventricular fluid is filled with blood, we find the tuft cells covered with blood pigment, and tumor cells may be found in the stroma of the chorioid plexus when we deal with

malignant tumors of the brain (sarcoma, carcinoma). When we speak of the function of the chorioid plexus, we have to take into consideration the stroma as much as the tuft cells.

Dr. Riley: I should like to ask Dr. Hassin how he would explain internal hydrocephalus arising through a tumor obstructing the aqueduct of Sylvius, on his basis of absorption rather than secretion by the chorioid plexus.

Dr. Hassin: The ventricular contents come from the perivascular spaces of the brain, which empty their contents into both the subarachnoid spaces and the ventricles. That the ventricles drain the brain substance, as does also the subarachnoid space, and that their contents are derived from the tissue fluids of the brain may be gathered from the experiments of Bruno, Putnam and Wislocki. From the ventricles, where the chorioid plexus absorbs certain substances from the ventricular fluid, the fluid is eliminated through the third ventricle, the aqueduct of Sylvius, the fourth ventricle and its foramina to the meningeal spaces; from the meningeal spaces it leaves the cranial cavity through other channels. When the aqueduct of Sylvius is blocked, the fluid keeps on accumulating and although the tuft cells continue to absorb certain substances from the accumulated fluid, the escape of the bulk of the latter by other channels is prevented and hydrocephalus is the result.

Dr. Globus: Dr. Hassin is, no doubt, familiar with the fact that the chorioid plexus is considered as a form of modified ependyma, and that the ependyma is a product of the early differentiated glia component of the central nervous system. It is understood that these ependymal cells acquire very early in their histogenetic process an epithelial character, a character of an excreting or a secreting cell. How can we say, then, that this essentially ependymal and important intraventricular structure has nothing to do with the fluid which is constantly being manufactured in the ventricular cavities?

Dr. Hassin's own slides have shown that the ependymal lining of the chorioid plexus has picked out certain particles and held them within their bodies, ready to allow them to be discharged into the cerebrospinal fluid. How can we get away from the conception that the chorioid plexus filters a certain fluid which forms a vehicle for the carrying away of the waste products of the central nervous system?

Dr. Hassin: I did not say that the spinal fluid is a vehicle; I did not say that at all. The ependyma as well as the tuft cells serve the same purpose—to filter the fluid that originates in the tissues of the brain. The latter discharges its waste through the perivascular spaces to the subarachnoid space and the cerebral ventricles. In the subarachnoid space the absorption or filtration takes place principally through the Pacchionian bodies, and in the ventricles it takes place through the ependymal and tuft cells of the chorioid plexus. The latter purifies, as it were, the fluid before it is eliminated.

Dr. Skoog: I should like to ask Dr. Hassin if he is aware of any pathological cases in which the chorioid plexus has been destroyed and the cerebrospinal fluid has been diminished in quantity or pressure. A few years ago I reported a case of central syphilis in which there was a marked destruction of many of the chorioid plexus cells, and previously two lumbar punctures had shown a very low cerebrospinal fluid pressure, something under 40 millimeters, only a few cubic centimeters of fluid being obtainable. Likewise, autopsy showed rather a dry subarachnoidean fluid system.

Dr. Hassin: Personally I have not had the opportunity to study such cases but I might refer to the investigations of Schmorl and Askanazy. These pathologists were the first to advocate the absorptive function of the chorioidal plexus. They showed that when the latter is damaged or destroyed by an infection or poison, the cerebrospinal fluid is abnormal chemically and in some instances a hydrocephalus results. Complete destruction of the chorioid plexus has been produced experimentally by Dandy. He excised the chorioid plexus from one lateral ventricle through a large incision in the cortex; blocked the foramen of Monro by a piece of fascia or peritoneum, and also obstructed the third ventricle. No fluid formed in the plexectomized ventricle, for the chorioid plexus that is supposed to elaborate it had been removed. However, an anatomical or histological description of the condition of the collapsed ventricle is not given by Dandy, and one might assume that marked reactive phenomena obtained in the ventricular cavity after stripping off the chorioid plexus, a large incision over the cortex and an insertion of a piece of tissue in the foramen of Monro. The result of these reactive phenomena was probably an obliteration of the lateral ventricle, and thus there was no room for the fluid to accumulate.

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Chapter XXIV

THE CEREBROSPINAL FLUID IN SYPHILIS OF THE NERVOUS SYSTEM

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THE first part of this article is devoted to the following brief historical account of the cerebrospinal fluid in syphilis of the nervous system:

The history of our knowledge concerning the cerebrospinal fluid in syphilis of the nervous system is practically that of the history of our knowledge of the pathological findings in the spinal fluid, because the majority of the early cases studied, which presented abnormalities, were cases of nervous system syphilis. As each new idea came into existence, it was in relation to syphilis; thus, the first important abnormal finding in the spinal fluid was that of an increased number of cells occurring in certain pathological conditions.

In 1901 Widal, Sicard and Ravaut,[1] and Nageotte[2] described the method of examining the cellular content of the spinal fluid by centrifuging and staining the sediment. They reported a hyperlymphocytosis in 90 per cent of their cases of tabes and paresis. Less frequently but often enough it was found also in the secondary and tertiary types of neurosyphilis. Two years later their observations were confirmed in Germany by Schönborn.[3]

In 1903 Ravaut[4] called attention to the finding of a pleocytosis in 42 per cent of 138 cases of secondary syphilis without obvious central nervous system involvement. He also occasionally found a pleocytosis in primary syphilis.

In the same year, Widal, Sicard and Ravaut[5] suggested that an increase in the albumin content of the spinal fluid was of significance. Guillain and Parant[6] separated the globulin from the albumin content by the use of magnesium sulphate, and emphasized the significance of the globulin. About the same time, Nissl[7] introduced the ammonium sulphate method for determining the presence of globulin.

The significance of finding a pleocytosis, with increased amounts of globulin and albumin in the spinal fluid, in cases of syphilis of the nervous system, was immediately recognized and led to numerous studies. In 1907 Alzheimer[8] introduced his method for the study of the spinal fluid, and much interest arose in the type of cell that appeared. This technique followed relatively soon after the important work of Nissl and Alzheimer concerning the plasma cell in paresis and tabes, and hence the interest in the cellular content of the spinal fluid was very great.

In 1908 Plaut[9] showed that spinal fluid could be used in place of blood serum in the performance of the Wassermann test. This was the first specific test for

syphilis of the central nervous system, and in many ways marked the most important advance made up to that time.

In 1912 Lange[10] described his gold sol test in connection with the investigation of the cerebrospinal fluid, thus introducing a new method of study; namely, the colloidal reaction. This is the last new departure in spinal fluid examination. Since 1912 we have acquired no new tests that add to our theoretical knowledge. Many modifications of each test have been offered. Time and space will not allow a consideration of all of these modifications, but a few may be mentioned. Thus, the cells today are usually counted in a specially devised counting chamber of the Fuch-Rosenthal type. A number of methods are available for the quantitative determination of albumin, the most satisfactory of which is probably that of Denis and Ayer.[11] Many tests for globulin have been advocated, such as the Noguchi butyric acid test, Pandy's carbolic acid test, and the Ross-Jones modification of the original ammonium sulphate test, the last being the one that is most frequently used. Numerous studies of the types of globulin found in the spinal fluid have been published. The fractional precipitation method shows the presence in the spinal fluid of globulin, euglobulin and fibrinogen, though no practical significance attaches to such determinations.

In connection with the Wassermann test, the modifications that have been used in the application of the Wassermann technique to the blood serum have also been applied to the cerebrospinal fluid. The important addition, however, is the introduction of the so-called "Auswertung Methode" by Hauptmann.[12] When Plaut originally described his technique, he was using 0.2 c.c. of cerebrospinal fluid. With this technique only about 60 per cent of the cases of cerebrospinal syphilis and tabes gave a positive reaction. Hauptmann showed that when one used 1.0 c.c. of spinal fluid in place of 0.2 c.c. a very much higher percentage of positive reactions occurred. Much information was obtained as a result of this, and the most satisfactory method at the present day is that of titrating the spinal fluid, using various dilutions.

Lange's colloidal gold test introduced an entirely new method. Numerous other colloidal tests have since been devised. Emanuel[13] showed that similar curves could be obtained by the use of gum mastic, and this method has been widely used, after having been modified by Cutting.[14] Kafka[15] still further modified the mastic test to give a color reaction, which he designated the "Normomastix" reaction. A great number of other tests have been described, such as the Berlin blue, congo red, hemoglobin, colloidal mercury, resin of podophyllin, resin of myrrh, gum lacque, elixir of paregoric, and collargol, etc.

The benzoin test as devised by Guillain, Laroche and Lechelle[16] has received a very great deal of attention in the last few years, and a modification, introducing a color reaction, has been studied by Thurzo.[17] No discussion of the relative value of these tests will be attempted but this résumé will suffice to emphasize again that no new idea of theoretical importance has come out of these various modifications or additional tests.

The investigation of the blood serum, with the object of finding a chemical or precipitation test, is paralleled by similar work with the spinal fluid. Various modifications of the Sachs-Georgi methods have been applied to the spinal fluid, without any notable success. Recently, Kahn,[18] whose test with blood serum has been very satisfactory, has made a preliminary report of a

similar technique for the spinal fluid, but as yet he has not obtained a satisfactory method.

Tests for various other chemical constituents of the spinal fluid have led to no important practical results. Thus, the spinal fluid sugar in syphilis of the nervous system is practically always within normal limits. However, it is of some interest to note, as shown by Alpers, Campbell and Prentiss,[19] that the sugar content in cases of general paresis at times runs quite high, as high as is the case in epidemic encephalitis, and, further, that in cases of general paresis there is a change in the sugar content as the result of antiluetic treatment.

Investigation of the salt content, the freezing point, the electrical conductivity, and the like, have been of no practical or clinical importance up to the present time.

The findings of spirochetes in the spinal fluid has been a matter of considerable theoretical importance, although it has had no marked practical application as a clinical procedure. In 1906, Hoffmann[20] produced experimental syphilis in a monkey with spinal fluid obtained from a case of early syphilis, thus showing that spirochetes entered the cerebrospinal fluid in the early stages of the disease. In 1913 Nichols and Hough[21] successfully inoculated a rabbit with spinal fluid obtained from a case of cerebrospinal syphilis.

Important Diagnostic Tests of Syphilitic Cerebrospinal Fluid

From the practical standpoint, there are five important tests to apply to the cerebrospinal fluid in cases of syphilis of the nervous system. These are (1) the Wassermann reaction, (2) tests for albumin, (3) tests for globulin, (4) the cellular content and (5) the colloidal gold test. In our own opinion, these five tests should be applied to every cerebrospinal fluid. There may be much variation in the exact methods utilized. Thus, one may use one technique or another for the Wassermann reaction. One may test for albumin with trichloracitic acid or alcohol, or quantitate the amount by one method or another. Any one of several tests may be used for globulin, and one or more of the colloidal tests may be employed. Our own preferences in this matter are as follows: For the Wassermann reaction a standard technique with a sensitive antigen should be employed and the fluid should be tested in titrations of from 0.05 to 1 c.c. The Denis-Ayer quantitative method for albumin and the Ross-Jones ring test for globulin should be used. The differential cell count should be made in a Fuch-Rosenthal counting chamber, the cells being colored with Unna's polychrome methylene blue; and the gold test should be performed according to the original Lange technique. The latter is recommended because of its relative standardization. It may be well to check this by either the mastic or benzoin reactions.

It will now be our endeavor to attempt to formulate with these tests the usual findings in the various types of syphilis of the nervous system, and to attempt to interpret their meaning.

The Spinal Fluid in General Paresis

The spinal fluid in general paresis is discussed first, because of the uniformity of the findings. The typical formula is indicated in Table XLI, and is found in practically every case of paresis.

Table XLI

Spinal Fluid Formula in General Paresis

Wassermann reaction	Cells	Total protein	Globulin	Gold sol	Remarks
Positive in 0.05 to 0.2 c.c. in 95 per cent. Slightly weaker reaction rarely found.	0–200+ Average, 25–50	50–150 mgms. per 100 c.c. Average, 89	+++	5432100000 5554321000 5555555555	(Unusually weak) (Average) (Unusually strong)

In fact, when this formula is not found in an untreated case, the assumption is almost certain that the case is not one of paresis. This statement may appear extreme, but it has been borne out by the experience of the majority of investigators dealing with the subject. There are, of course, some exceptions: a couple of cases have recently come to autopsy in which the histological findings suggested paresis, and yet the spinal fluid formula was not quite so strong as that indicated here. These cases, however, have been exceedingly few in number and in them there remains some doubt, even after the histological examination, as to whether the process was really one of general paresis or cerebral syphilis. If one bears in mind the difficulty of making a histological differentiation between these two conditions, one sees how unsatisfactory it is to attempt to be absolutely dogmatic in regard to constituents of the spinal fluid. Yet, from the practical standpoint, a vast majority of cases of general paresis give this type of reaction, so that when it is not present, the chances are that the case is not one of paresis. Of course, this does not hold for cases that are having treatment. The important point about this formula is

that the Wassermann reaction is positive with 0.05 to 0.2 c.c. of spinal fluid. The gold curve, or other colloidal curves, give a strong reaction. If the gold solution is considered, one should obtain a reaction beginning with a full precipitation in the first tube and continuing for three or four tubes before it weakens. The cell count is usually under 50, but in exceptional cases it may go as high as a couple of hundred per cubic millimeter. However, when the cell count is above 100 per cubic millimeter, one has a right to feel that there is a greater degree of meningitis than is commonly found in paresis (see the discussion of the significance of the cell count). The globulin and albumin should be present in considerably increased quantities.

The Spinal Fluid in Tabes Dorsalis and Cerebrospinal Syphilis

Despite the close relationship between paresis and tabes, both being types of parenchymatous syphilis, the results of investigations of the spinal fluid in tabes are more similar to those of the meningovascular type than to those of paresis, and the formulae may be considered together. Table XLII gives a typical formula:

Table XLII

Spinal Fluid Formulae in Tabes Dorsalis and Meningovascular Syphilis

Wassermann reaction	Cells	Total protein	Globulin	Gold sol
Positive in 0.05–1.0 c.c. 40 per cent neg. with 0.2 c.c. Pure vascular neurosyphilis usually negative with 1.0 c.c.	Tabes, 0–200+. Average, 25–50	17–150 mgms. per 100 c.c. Average, 78	0 to ++++	0122100000 0134431000 3332100000 4443210000 5431000000 5555431000
	Meningovascular and acute meningitis, 200–2000	Average, 99 mgms. per 100 c.c.		
	Chronic, 0–200+	Average, 73 mgms. per 100 c.c.		
	Vascular, often no increase.			

The characteristic feature of this formula which differentiates it from that of general paresis is that the Wassermann reaction is weaker, often being negative, with 0.4 or even 0.6 c.c. of cerebrospinal fluid. It is of interest to note that when Plaut first published his findings, using 0.2 c.c. of cerebrospinal fluid for his test, he stated that about 40 per cent of the cases of tabes and of cerebrospinal syphilis gave negative Wassermann reactions. This is about the percentage that subsequent investigation has shown to be negative when a small amount of fluid is used. The colloidal gold curve is typically weaker than that found in paresis and is further characterized by the fact that the curve begins with a moderate precipitation in the first tube and then becomes weaker, or begins with very slight or no precipitation in the first tube and becomes stronger through two or three tubes and then weaker, the last tubes being unaffected. In tabes the cell count is very much the same as that found in paresis, although there is often some difference in the type of cells present. In the meningeal forms of syphilis, particularly that of spinal meningitis or acute meningitis, the cell count may be very high, reading into the thousands, containing relatively few endothelial cells and only rarely plasma cells, the majority of cells being small lymphocytes with possibly 20 per cent large lymphocytes, and a few polymorphonuclear leucocytes, especially in those cases where the cell count is very high.

Table xliii

Variations of Spinal Fluid Reactions in Tabes Dorsalis*

	Wassermann reaction	Cells	Total protein, mgms. per 100 c.c.	Globulin	Gold sol	Remarks
1	Positive, 0.6 c.c.	25	70	++	0244310000	Average
2	Positive, 0.05 c.c.	75	95	+++	5555421000	Not rare
3	Positive, 1.0 c.c.	40	30	+	negative	Relatively inactive
4	Negative	50	50	++	0244310000	Infrequent
5	Positive, 0.4 c.c.	4	25	+	negative	Infrequent
6	Negative	30	35	+	negative	Infrequent
7	Negative	3	17	0	negative	Burned out or stationary

* Other variations are also found.

Table XLII gives the typical findings in tabes dorsalis and the meningovascular types of neurosyphilis. However, while they are typical and thus may be differentiated from general paresis, it does not follow that this is the formula that is obtained in the majority of cases. The variations run in both directions (Tables XLIII and XLIV).

TABLE XLIV

VARIETIES OF SPINAL FLUID REACTIONS IN MENINGOVASCULAR SYPHILIS*

	Wassermann reaction	Cells	Total protein, mgms. per 100 c.c.	Globulin	Gold sol	Remarks
1	Positive, 0.6 c.c.	90	70	++	0244310000	Average
2	Positive, 0.4 c.c.	1200	118	++++	4443210000	Acute meningitis
3	Positive, 1.0 c.c.	2	45	+	0122100000	Pure vascular
4	Positive, 0.05 c.c.	40	130	+++	5555431000	Paresis sine paresi. Asymptomatic
5	Positive, 1.0 c.c.	10	30	+	1233210000	Mild
6	Negative	35	35	+	Negative	Mild meningitis
7	Negative	75	50	+	4443100000	Infrequent

* Many other combinations are also found.

There are plenty of instances of cases of tabes and cerebrospinal syphilis giving a so-called paretic formula. This is to be noted in cases of meningeal involvement occurring in the secondary stage of the disease, and as it has been so often misinterpreted, it will be discussed in more detail below. On the other hand, there are many cases of tabes and meningovascular syphilis in which the findings in the spinal fluid are very weak. In perfectly clear-cut cases of tabes and meningovascular syphilis, only one or two of the five tests under discussion will be positive, whereas the others will be negative. This matter was discussed in some detail by the present writer,[22] in a paper in 1920, called "The Nonconcomitance of Spinal Fluid Tests." Thus, one finds instances of either tabes or meningovascular syphilis in which the only positive finding is a pleocytosis; or in other instances, the Wassermann reaction will be positive and all other tests negative, or the globulin and

albumin will be the only positive tests, while in some cases only the colloidal tests are positive. This nonconcomitance of the spinal fluid reactions is shown also in cases undergoing treatment, where one test or another becomes negative first, leaving an incomplete formula, and finally, as serological recovery occurs, there may be but one test remaining positive.

Finally, it is to be noted that there are cases of active neurosyphilis in which all these tests are negative. Discussion of this matter was presented by the present writer[23] in association with J. V. Klauder in 1921.

To summarize this section, it may be stated that in tabes dorsalis and meningovascular syphilis, the spinal fluid results vary a great deal, all the way from a strong reaction of the variety found practically always in cases of general paresis, to an entirely negative fluid.

The Spinal Fluid in Early Syphilis

As already mentioned, Ravaut,[4] as early as 1903, called attention to abnormalities in the cerebrospinal fluid in the primary and secondary stages of syphilis, referring chiefly to a lymphocytosis, and in 1906 Hoffmann[20] showed that spirochetes might be circulating in the cerebrospinal fluid in the very early stages of the disease. In 1915 Wile and Stokes[24] discussed at length the presence of abnormal cerebrospinal fluid findings in the primary and secondary stages. In 1921 Wile and Hasley[25] found spinal fluid abnormalities in 22 per cent of a series of 221 cases of early syphilis, even observing a positive spinal fluid Wassermann reaction prior to the appearance of this result in the blood stream. In 1918 Cornaz[26] found that in 35 per cent of the cases of early syphilis a pleocytosis had occurred before the appearance of cutaneous or mucous lesions. In 1919 Nicolau[27] studied 51 cases of primary syphilis prior to the appearance of secondary manifestations. In 18 the spinal fluid showed a definite lymphocytosis. Similar results have been reported by McIver,[28] Klauder,[29] Scott and Pearson,[30] and Larkin and Cornwall.[31] From the theoretical standpoint, these observations are of great moment, indicating the frequency with which the central nervous system is involved in the early stages of syphilis. Moore[32] has epitomized this theoretical problem as follows: "The percentage of patients thus found to have early fluid abnormalities approximates the incidence of late clinical neurosyphilis—one fact which makes it probable that when central nervous system invasion does take place it practically always occurs during the

first months of the infection rather than at some later period." It is our own belief that this is approximately a correct presentation. It has not been absolutely proved at the present time, and we have evidence that occasionally a later invasion does occur. Nevertheless, this is a very important view from the practical standpoint, as it means an early examination of the spinal fluid in every syphilitic individual; and it is undoubtedly true that the majority of cases of symptomatic neurosyphilis in which the symptoms occur five to thirty years after the infection have shown positive results in the spinal fluid during practically the entire course of the infection. No definite formula can be given for the constituents in the early stages as they vary a great deal, according to the type of involvement. It may be said that in the majority of cases of early syphilis the abnormal findings are of a mild nature. There is one group of early cases in which the fluid is characterized by the appearance of globulin, an increase in protein and an increase in the cell count, a weak colloidal gold test, or a weak Wassermann reaction. Any one or several or all of these tests may be positive, but may only give slight reactions. Then, another somewhat smaller group will show relatively strong reactions. In some cases of this group there is a strong Wassermann reaction in the absence of all other spinal fluid abnormalities or there may be several tests strongly present and one or two weak, or they all may be moderately strong. Finally, there is a smaller group in which the formula is practically the same as that found in paresis. This matter has been very well described by Dr. Moore[32] in the article already mentioned, and has the utmost significance in the matter of classification and treatment. Table XLV represents types of fluid found in the early stages. These are taken from the article by Moore.

TABLE XLV

SPINAL FLUID EXAMINATIONS FROM CASES OF EARLY SYPHILIS

Wassermann reaction	Cells	Globulin	Gold sol	Mastic
Negative	10	++	2211100000	3221000000
Negative	21	+	0011100000	2210000000
Positive, 1.0 c.c.	8	++	3433210000	5543200000
Positive, 0.2 c.c.	14	+++	2222200000	4322200000
Negative	4	±	4433321000	4321000000
Positive, 0.2 c.c.	98	+++	5555543000	5532100000

Interpretation of the Five Tests

The Wassermann reaction is the only test which is definitely specific for syphilis. The other tests merely suggest inflammatory or degenerative lesions of the central nervous system. The colloidal tests, however, have a considerable degree of specificity, but are by no means as specific as the Wassermann reaction.

1. THE WASSERMANN REACTION

The exact basis for the positive Wassermann reaction in the cerebrospinal fluid is no more clear than it is for the blood serum. It is not known what causes this reaction. Nevertheless, a consistently strong positive Wassermann reaction in the cerebrospinal fluid is definite evidence of syphilis of the nervous system. It is possible that the positive reacting bodies in the blood stream may be carried into the cerebrospinal fluid without the presence of spirochetes within the central nervous system, but this is a possibility which as yet has not been disproved, and there is no good evidence in favor of it. In a majority of cases giving a positive blood Wassermann reaction, the spinal fluid is negative. We are, therefore, ready to believe that the hematocephalic barrier is capable of preventing the passage of these bodies. In those cases in which there might be a break in this barrier which would allow these bodies to be carried over, it is highly possible that the spirochetes themselves would also enter the nervous system. While there is a theoretical possibility of a positive spinal fluid Wassermann occurring without the entrance of the organism into the cerebrospinal system, it is easy to meet this speculation by arguments which are equally potent. In practical and clinical experience there is but little evidence that this ever occurs. It may, therefore, be assumed for practical purposes, that a positive Wassermann reaction in the cerebrospinal fluid represents a spirochetal lesion within the central nervous system. Attention has been called to the fact that the strength of the spinal fluid Wassermann reaction varies considerably in different cases. The reason for this is by no means clear. Experience has taught us that a strongly positive spinal fluid Wassermann, that is, positive with from 0.05 to 0.2 c.c., is characteristic of cases of general paresis. Furthermore, it is known that the patients who give a strongly positive spinal fluid Wassermann reaction are more resistant to treatment than are the cases giving weak reactions. This, however, is only a general

truth and has many exceptions, for at times one finds a strongly positive spinal fluid Wassermann becoming negative with a relatively small amount of treatment. This is true in certain early acute cases of cerebrospinal syphilis as well as in some late cases of meningovascular syphilis. On the other hand, there are many cases of tabes in which the Wassermann reaction is positive only with 0.8 c.c. and negative with 0.6 c.c. and in which much treatment does not modify the reaction. It has been stated that cases of pure cerebral syphilis, that is, cases in which there is no spinal involvement, are likely to give weaker reactions than those in which the involvement occurs in the spinal portion of the nervous system. This has not, however, been definitely established. The explanation of a negative spinal fluid Wassermann reaction in active neurosyphilis, with some or all of the other tests positive, is not forthcoming. In our experience, this phenomenon occurs in all types of neurosyphilis with the exception of general paresis.

2. THE CELLULAR CONTENT OF THE SPINAL FLUID

The presence of a pleocytosis in the spinal fluid is indicative of an irritative or inflammatory lesion of the brain, spinal cord or meninges. The number and the type of cells give some basis for diagnostic interpretation, but cannot be used in a dogmatic fashion. It is probable, although not proved, that the cells found in the spinal fluid for the most part have their origin in the meninges, although it is also possible that some cells from the perivascular infiltrations in the true nervous substance also are poured into the cerebrospinal fluid and make their way to the lumbar sac. The majority of cells, however, that one obtains from lumbar puncture fluids, are probably cells which have originated from the spinal meninges. The length of time that a cell cast off into the cerebrospinal fluid will retain its shape and characteristics has not yet been determined.

In regard to this question, some work of interest by Young and Alpers[33] has emanated from our laboratory. As is well known, a subarachnoid injection of Swift-Ellis serum will produce a pleocytosis which on the day following the infection may be as high as a thousand cells or more. Some time between thirty-six and forty-eight hours after the injection it is frequently found that the cell count has returned to its base level. In other words, the cells are no longer found floating freely in the fluid, but whether these have been autolyzed, or plastered to the meninges, or have made

their way out of the fluid is not clear. However, their relatively rapid disappearance suggests that cells emanating from the cerebral meninges or cerebral perivascular spaces may not be recovered by lumbar puncture.

It is usually assumed that a high cell count is indicative of a marked meningitis. Within limits this is probably true. Certainly the acute meningeal reactions, particularly those affecting the spinal meninges, will give a high cell count, which may reach one or two thousand cells per cubic millimeter. However, when dealing with relatively smaller numbers of cells, that is, with cell counts varying from 0 to 100 per cubic millimeter, no such conclusions are justified. We have previously called attention to the fact that cases of paresis showing a normal cell count may, at autopsy, show a fair amount of cerebral meningitis; whereas cases showing a cell count considerably above the normal may exist with a very mild meningitis.[34] Therefore, the fact should be emphasized that in dealing with cell counts between one and two hundred per cubic millimeter it is not justifiable to draw clear-cut conclusions as to the existence or non-existence of a relatively marked chronic meningitis. However, experience seems to justify the conclusion that where the cell count is above 200 per cubic millimeter, it is probable that one is dealing with an active meningitis, a large portion of which is usually spinal. Experience also teaches that it is relatively infrequent in cases of uncomplicated general paresis or tabes to find a cell count in the neighborhood of 200 per cubic millimeter, and where such a high cell count exists, one may assume for clinical purposes that one is dealing with a relatively marked meningeal process, which, however, may be superimposed upon a true underlying paretic or tabetic condition.

The character of the cells found in the spinal fluid has some significance. In cases of neurosyphilis the predominating cell is the small lymphocyte, with from 10 to 25 per cent of large lymphocytes. In very acute syphilitic cerebrospinal meningitis as many as 25 per cent of polymorphonuclear leucocytes may be present. In all other types of neurosyphilis the polymorphonuclear leucocytes are very infrequent, rarely rising above 2 or 3 per cent. The plasma cell, when present, is of considerable significance. In cases of general paresis, particularly where there is a fair number of cells, one will usually, though not by any means always, find from 2 to 5 per cent of plasma cells. Plasma cells, on rare occasions, appear in small numbers in cases of tabes, and are extremely infre-

quent, if ever present, in cases of pure meningovascular syphilis. A variety of odd-shaped cells, probably of the endothelial series, may be found in the spinal fluid, especially in cases of well-advanced paresis. These cells present a great many different forms. Gitter cells, or large vacuolated cells, are frequently found in the late stages of general paresis and very much less frequently in other types of neurosyphilis. These cells have been beautifully pictured in the monograph by Plaut, Rehm and Schottmüller.[35] Cells of this type are also found in all varieties of relatively chronic meningitis; that is, they are found in slow-running meningitides of staphylococcic or other pus-forming organisms. The cell count may be within normal limits in all varieties of neurosyphilis, with the exception of active spinal meningitis.

3 AND 4. TOTAL PROTEIN AND GLOBULIN

These two elements may be considered together, as globulin is a protein and when present adds to the total amount of protein found. An increase of protein and the presence of globulin are indicative merely of a disorder within the nervous system and are by no means diagnostic of syphilis, as they occur in hemorrhage, tumors, etc. Globulin and an increase in the protein are practically always found in cases of general paresis. The more active the process, as a rule, the larger the amount of these substances. They are usually found in active cases of tabes, but it must be borne in mind that there are active cases of tabes with a positive Wassermann reaction, gold sol and pleocytosis, in which there is no evidence of globulin by the usual tests, and in which the total protein is within normal limits. The same is true, even more frequently, in cases of cerebrospinal syphilis. But in the majority of cases of neurosyphilis where a pleocytosis is present, globulin and increased albumin are also found. As a rule, the amount of globulin and total protein is greater in general paresis than in the other types of neurosyphilis, with the exception of the very acute meningitides.

5. COLLOIDAL GOLD TEST

The colloidal gold test, being the first colloidal test to be discovered, and the one with which we have had the most experience, is discussed as the paradigm for the colloidal reactions. The reason for the reactions obtained with spinal fluid is not known. The present situation is entirely empirical. The most frequently advanced

explanation of the reaction is that it depends upon the presence of globulin, or, at any rate, on the ratio between globulin and total protein. But, as has been pointed out by the writer and many others, at times a very strong gold reaction occurs when the presence of globulin cannot be determined by Noguchi's butyric acid test, the ammonium sulphate or other clinical tests. Judging from an abundant experience, however, it is possible to draw some conclusions about the tests that are of value in diagnosis. The most interesting phenomenon is that, with the technique suggested by Lange, the syphilitic cases, when they do give a reaction, always give the height of their reaction in the first five dilutions. Unfortunately, however, for the specificity of this test, other conditions occasionally give reactions in this same area. The paretic cases almost without exception give a typical reaction, beginning with a complete precipitation in the first tube. This led the early workers with this method to coin the term "paretic curve," which is a misnomer because it is by no means pathognomonic of paresis. The literature contains much discussion as to whether or not a case of neurosyphilis giving a so-called "paretic curve" is to be considered as a case of paresis. Writing on this subject in 1915, the present writer[35] drew the following conclusions: Fluids from cases of general paresis will give a strong and fairly characteristic reaction. Very rarely fluid from a case of general paresis will give a reaction weaker than the characteristic one. Fluids from cases of syphilitic involvement of the central nervous system other than general paresis often give a weaker reaction than the paretic type of reaction, but in a fairly high percentage of cases give the same reaction as do the paretic fluids. Non-syphilitic cases may give the same reaction as do the cases of paresis. When a syphilitic fluid does not give the strong "paretic reaction," it is good presumptive evidence that the case is not one of general paresis. The term "syphilitic zone" is a misnomer. These conclusions, we believe, are justified by later experience. In 1921 a review of the gold tests made in our laboratory was reported by Thompson.[37] This was based upon the examination of over eight thousand cerebrospinal fluids. His conclusions as to the value of the test, we believe to be correct, and they may be summarized as follows: The vast majority of cases of paresis give a "paretic" gold reaction. The presence of "paretic" curves in almost 50 per cent of the cases of cerebrospinal syphilis shows that the presence of such curves does not differentiate cerebrospinal syphilis from paresis. Such

curves occur in multiple sclerosis, tabes, brain tumor, etc. Practically identical conclusions have been reached by other workers in this field, notably Kafka[38] and Weigeldt.[39]

Unquestionably, one of the most important practical points that have been brought up in regard to the spinal fluid data in syphilis of the central nervous system relates to this so-called "paretic curve." It may, therefore, be in order to produce some of the facts on which we base our statement that this curve in cases of neurosyphilis is not pathognomonic of paresis. It is found in cases of early syphilis, that is, in cases in the secondary period, which can, only by an unjustified stretch of the imagination, be considered as true paresis. It occurs in many cases which have the characteristic symptomatology of meningovascular syphilis and tabes dorsalis, with no symptoms suggestive of true paresis. Many of these cases clear up symptomatically and serologically under treatment in a way that is quite inconsistent with our concept of the reaction of paresis to treatment. The "paretic curve," as a matter of fact, is merely a stronger reaction than one finds in many cases of neurosyphilis. One must bear in mind that the test, as conventionally performed, begins with a dilution of spinal fluid in saline of 1 to 10. In this dilution, cases giving the so-called paretic curve give a complete precipitation, whereas cases giving the syphilitic non-paretic curve do not give full precipitation in this tube or may give no precipitation. As the curves are plotted, they show marked differences. However, if one uses lower dilutions, that is, 1 to 5, 1 to 3, 1 to 2, 1 to 1, or 2 to 1, it is found that the paretic curve is quite symmetrical and quite comparable to the other curves, only giving a stronger and more intense reaction. It may, therefore, be concluded that the difference between a paretic and non-paretic syphilitic curve is one of degree and not of kind; that is, it is quantitative rather than qualitative. Thus it follows in line with what has already been seen to be the case in regard to the strength of the Wassermann test and the amount of globulin and albumin that is usually found in these conditions. The paretic curve, therefore, is indicative of a relatively marked reaction and it usually suggests that therapy will be difficult, but, as has already been noted, this is not always the case. What has been said in regard to the gold test is true of the other colloidal tests as well, and although claims have recently been brought forth that the benzoin test will give a differentiation both as to the luetic and non-luetic, as well as the differentiation of paretic and non-

paretic conditions, it is believed that these have not been established up to the present time.

Negative Spinal Fluid in Neurosyphilis

There are cases of neurosyphilis in which the cerebrospinal fluid is entirely negative so far as the tests under consideration are concerned. The discussion of this in some detail was presented by Solomon and Klauder in 1921. It has been recognized, of course, that there are cases of so-called "burned-out" neurosyphilis, particularly cases of burned-out tabes in which the tests are all negative. Also it is frequent to find active cases of purely vascular neurosyphilis in which the spinal fluid is negative. In addition to these types, there are other cases of neurosyphilis in which, despite a negative fluid, the activity of the pathological process still goes on. This is well shown by cases which we have described in referring to provocative reactions in the cerebrospinal fluid in neurosyphilis. Here cases were presented that had symptoms of activity in which the spinal fluid was negative, but in which it became positive after treatment. It is by no means infrequent to see cases of clinical neurosyphilis with a negative spinal fluid in one examination, which at a later period presents positive results. There are also cases of tabes in which, despite the negative character of the spinal fluid, abundant evidence of activity of the disease may be adduced. In fact, it has been pointed out by Richter that a true tabetic process is a single degenerative lesion and that the meningeal process is superimposed.

Cerebrospinal Fluid from Different Loci

The question of a difference in the constituents of the spinal fluid from different loci is discussed in detail in another portion of this chapter. It is in place here, however, to note that the ventricular fluid in many cases differs from the fluid from the lumbar subarachnoid space. In 1915[39] attention was called to the fact that the gold reaction was applicable to post-mortem fluids and that in the examination of fluids from different loci, including the ventricles, the base of the brain, and cisterna magna and the lumbar subarachnoid space, there was considerable variation in the reaction; whereas the reactions were of the so-called "paretic" type in the fluid from the lumbar region. Subsequent experience with fluids obtained from paretics who had been trephined, showed

that the ventricular fluid was entirely negative at times, whereas the spinal fluid would present the usual reactions. In other cases, the ventricular fluid gave milder reactions than the spinal fluid, but in the majority of cases, the ventricular and spinal fluids were of similar composition. This matter has recently been discussed by Cestan, Riser and Péres,[40] who find this same variation. They emphasize the conclusion that no deductions of any clinical importance can be drawn from this except the fact that ventricular puncture would have little or no advantage in making an early diagnosis. This has interest in relation to the question of the circulation of the cerebrospinal fluid and opens up several important questions for investigation. It is not known whether the positive data obtained from the ventricular fluid in certain cases represent a specific ventriculitis, or whether they represent a dilatation of the outlets from the ventricular system, thus changing the circulatory phenomena and allowing a backwash of fluid into the ventricles. In an earlier report on the provocative reactions in the cerebrospinal fluid, attention was called to the fact that a ventricular fluid which was negative in a case of paresis became positive after a ventricular injection, with recovery of the patient symptomatically and, later, serologically.

The Spinal Fluid in Congenital Neurosyphilis

What has been stated regarding the spinal fluid in neurosyphilis holds in every detail for the fluid in congenital neurosyphilis, so far as our knowledge and experience have taken us. Cases of congenital paresis give the same formula as do cases of acquired paresis. In one case of juvenile tabes that we have followed, the fluid evidence was of the type usually found in acquired tabes. In cases of asymptomatic congenital neurosyphilis, we have found several different formulae; that is, in some cases the findings are very mild in one test, but positive or negative in various others. Further, we have found cases of asymptomatic neurosyphilis with paretic formulae, which were very obstinate to treatment. Finally, in children under two years of age, we have found the paretic formula occurring in conjunction with convulsions, hemiplegias and other similar manifestations that are not readily confused with the symptoms of paresis and that occur in the time period which would make paresis not to be too strongly considered.

The Effect of Treatment on the Cerebrospinal Fluid Evidence

This is such a complicated subject that a complete presentation cannot be made within the limits of the available time and space, and a general discussion of our conclusions without presentation of full data must suffice. In cases of neurosyphilis receiving treatment, where improvement occurs it is frequently found that the serology approaches a negative condition more or less coincidentally with the clinical improvement. This, however, is not universal, and there are cases in which serological recovery occurs with no concomitant clinical improvement. More frequently, one finds clinical improvement without serological change, or with only a moderate improvement in the serology. This statement holds for all varieties of neurosyphilis and all varieties of treatment. It is a well-recognized fact that cases of meningovascular syphilis are the most easily affected by treatment, and that cases of paresis are the most resistant. Similarly, the cerebrospinal fluid in cases of meningovascular syphilis most readily return to normal, whereas with the paretic fluid this return is much more difficult and far less frequent. The tabetic cases are mid-way between these two. Since, as already noted, many cases of meningovascular syphilis and tabes give relatively mild spinal fluid reactions compared with those in cases of paresis, it therefore follows that the weaker spinal fluids are more usually returned to normal than are the stronger. It must be emphasized, however, that there are many instances in which the very strong so-called paretic formula is returned to normal with a relatively small amount of intravenous arsphenamine, whereas much weaker fluids in cases of meningovascular syphilis are absolutely resistant to intravenous therapy and often resistant to subarachnoid therapy. In order to make our position thoroughly understood, it should be stated at this point that we believe that subarachnoid therapy is usually more efficient in the treatment of cases of meningovascular syphilis and tabes than is intravenous therapy, and, further, we maintain that a true paresis may be arrested and the spinal fluid brought to a normal type of reaction. As these are controversial points, we can do no more than call attention to our own position in this, which must necessarily affect our attitude toward the question of the reaction of the spinal fluid to treatment.

In dealing with the cases in which the spinal fluid becomes normal, there is no uniformity of opinion in the literature as to which tests

are most easily affected, and which are most resistant. It has been frequently stated that the colloidal gold is the most resistant. Other authors have stated that the Wassermann was the most difficult to change, and still others have maintained that the globulin is the most stationary. In general, there is some uniformity of opinion that the cell count is the most easily brought within normal limits. That this is so with tryparsamide treatment seems to be without question. It is almost, although not absolutely universal, for the cell count may become normal after six to twelve injections of tryparsamide, irrespective of any other changes in the cerebrospinal fluid, and the same is relatively true for other types of treatment. Our own point of view concerning the changes of the other constituents is that which we enunciated in a paper on the "Nonconcomitance of Spinal Fluid Tests."[22] At this time we stated that under treatment in certain cases the gold sol reaction was the first test to change, in others the last, and so with the other tests. We stated at that time: "In neurosyphilitic cases receiving treatment these substances (the reagents providing the five tests under consideration) disappeared at different rates which vary in different cases, so that no general law can be laid down as to which element is the most easily affected by treatment in any particular case, though in general the pleocytosis disappears first." It is our belief that a tremendous series of cases carefully divided according to serological findings and clinical diagnoses would have to be thoroughly studied before any general conclusions would be justifiable. It should merely be reiterated that there are cases in which every test, with the exception of the Wassermann, has been returned to normal; in other cases where the Wassermann was the first test to become normal, all of the others remained positive; and likewise with each test, and with the pleocytosis. Further, the evidence of the provocative effect of treatment on the spinal fluid constituents is frequently noted in the treatment of cases showing relatively mild serological reactions. Not infrequently these tests will become strongly positive after a small amount of treatment, either intravenous or intraspinal, whether with arsphenamine or tryparsamide. It is, in fact, extremely frequent to find with tryparsamide that a moderately strong gold becomes a "paretic type" after a few injections of the medicinal agent. Further, it should be noted that when frequent spinal fluid examinations are made of patients under treatment, the tests will vary greatly from week to week or even from day to day. Cases that

show all of the tests to be negative on one occasion may show all of them strongly positive no longer than three days later. With this phenomenon we have had much experience, not to say many heartbreaks. Explanation of this is not easy to offer, but it quite parallels the situation in regard to the Wassermann in the blood serum where one day the test may be negative and the next day positive. It is of more interest in the spinal fluid because here we have five tests, rather than one, and here again we find one, or several, or all, that act in this fashion. It is easy to offer possible explanations, but all such attempts are purely speculative and entirely unproved.

Discussion

The following questions submitted to Dr. Solomon before the Commission, together with the answers to them, are here reported verbatim.

Dr. Jelliffe: We know that Nonne first reported that in certain cases of multiple sclerosis a positive Wassermann may be found; then we later learned from Dr. Ayer, that in multiple sclerosis the so-called paretic gold sol curve was not infrequent; and, as we have had reported this morning by Dr. Patten, in about 50 per cent of cases of multiple sclerosis there is a positive gold sol curve. Also Kuhn and Steiner published their results and said that they found a spirochete in multiple sclerosis, and some people have been quite pleased with the discovery and say, "At least we have found out all about multiple sclerosis: it is a spirochetal infection, and that is all there is to it."

But there are others who maintain that multiple sclerosis, being a syndrome, may have many etiological factors, of which the Kuhn and Steiner spirochetes may only be one.

My question is whether it is logical to assume that those cases, in which there was a positive Wassermann, and a positive gold sol curve, might be cases of Kuhn and Steiner spirochetal multiple sclerosis?

Dr. Solomon: I can only answer Dr. Jelliffe by saying that his is a very enlightening, stimulating and happy speculation, but I am entirely unable to answer it.

Dr. Meyer: Would it not be better to ask the question as follows: Is there any specific globulin or protein reaction with spirochetes, as opposed to other forms of organisms?

Dr. Solomon: I wish that I could answer Dr. Jelliffe's question but I cannot, so I will have to ask Dr. Meyer to answer his own and Dr. Jelliffe's question.

Dr. Meyer: I cannot answer the question in any other way than by saying that we have evidence of the so-called paretic curve, where we have very good reason to assume that there is no spirochetal process action as a causative agent.

Dr. Solomon: I can add that we do see paretic curves occurring occasionally in cases of brain tumor, in cases of epidemic encephalitis, occasionally in cases of meningitis, although very rarely; so that I believe that the reaction possesses no specificity in regard to any particular disease or etiological agency.

Dr. Barker: Has Dr. Solomon or any one present ever seen a positive Wassermann in the fluid of a case of multiple sclerosis, where syphilis was not actually existent? I am very doubtful if a positive Wassermann ever occurs in multiple sclerosis except when there is also syphilis.

Dr. Solomon: I have never seen a case of undoubted or uncomplicated multiple sclerosis in which the spinal fluid Wassermann reaction was positive.

Dr. Jelliffe: That is the point that Nonne made, that with all the other results negative, he did find a positive Wassermann, and he therefore said these were non-syphilitic multiple sclerosis cases. Other cases with other positive specific symptoms were cases of syphilitic multiple sclerosis.

Dr. Jones: I am very interested in these results of the gold sol reactions in connection with the paper presented by Miss Cockrill, and I should like to ask Dr. Solomon if any of these colloidal reactions performed with the benzoin test have been compared with the gold sol test and what the results are?

Dr. Solomon: We have not used the colloidal benzoin. We have used the mastic solution and the results compare very closely with those found in the colloidal gold solution.

Dr. Menninger: Are the cerebrospinal fluid findings of congenital neurosyphilis generally as strong as those of acquired neurosyphilis?

Dr. Solomon: My impression is that the reactions in congenital and acquired neurosyphilis are very similar and of equal strength. For instance, in juvenile paresis the curves are practically the same as in the paresis of acquired syphilis. Similarly, in tabes they are apparently identical.

Dr. Osnato: Is Dr. Solomon in a position to give us any data on the spinal fluid findings in congenital syphilis?

Dr. Solomon: We have examined a great many cases of congenital syphilis and in the majority, as in acquired syphilis, perfectly normal spinal fluids are found. About 20 to 30 per cent of the cases of congenital syphilis show abnormal findings in the spinal fluid, and they are very variable in reaction: from a few cells to the typical strong paretic type of response.

Dr. Osnato: What about the blood Wassermann in cases of congenital syphilis?

Dr. Solomon: As in acquired syphilis, so in the congenital form, the blood Wassermann reaction may be either positive or negative. In early life it is more likely to be positive than at adolescence or later.

Dr. Craig: If Dr. Solomon designates the gold curve in paresis "strong" and the curve in cerebrospinal lues "weak," how would he designate the curve often found in acute meningitis, which begins low and runs up, the reverse of the paretic curve?

Dr. Solomon: I did not mean to introduce a new nomenclature in the reading of the gold curve. I merely wanted to call attention to the fact that the difference between these two varieties of curves was that one was stronger than the other. I think, as a matter of fact, it would be very much better if we spoke of curves in the lower or higher dilutions, and of strong or

weak reactions in low or high or mid-zone dilutions. Everybody knows perfectly well that all varieties of inflammatory lesions of the nervous system at times give curves in the lower dilutions. It is not specific for lues, although lues practically always gives these reactions in the lower dilutions.

Anyone who has had a large number of cases of syphilis of the nervous system has found cases in which, for some reason or other, he did not get the curve in the typical region; it often moves over a bit. I believe it is much wiser to speak about a strong reaction or a weak reaction in the low dilution or in the mid-zone of the table, or at the end. To a large extent this is the type of observations which Lange originally made.

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Chapter XXV

THE STUDY OF THE CEREBROSPINAL FLUID IN CASES OF BRAIN TUMOR*

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I. Introduction

THE value from a diagnostic standpoint of a systematic study of the cerebrospinal fluid is established beyond doubt in the fields of neurosyphilis and the acute inflammatory processes. Many consider it to be helpful in a few of the chronic degenerations of the central nervous system, most notably multiple sclerosis. There have been but few extensive investigations carried on to ascertain the changes, if any, in cerebrospinal fluids in brain tumors. Perhaps this is to be accounted for by the fact that lumbar puncture is known to be a dangerous procedure in advanced cases with foraminal herniation.

Of the observations made on the cerebrospinal fluid in brain tumor, those of Lange[1] are significant. This author in 1912 studied the gold sol reaction in five spinal fluids obtained from cases of brain tumor. He stated that tuberculous meningitis, brain tumor and hemorrhages into the subarachnoid spaces or ventricles all produced a spinal fluid showing the same gold curve. In a more recent contribution Lange[2] seeks to establish from a series of 60 cases a definite picture of the spinal fluid from cases of brain tumor. This picture includes the following essentials:

1. A typical gold curve with color changes occurring in the dilutions above 1:80.

2. A moderate increase in total protein values. (Normal value equals 20 mgms., while the average brain tumor value equals 40 mgms. per 100 c.c. of spinal fluid.)

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3. The almost invariable yellow coloration of the spinal fluid.

He also states that the picture is only diagnostic of brain tumor when old hemorrhages due to trauma, apoplexy, operation or puncture are excluded, for these old hemorrhages give a picture identical with that obtained in the spinal fluid from cases of brain tumor.

Moersch[3] reviews a series of 127 proved cases of brain tumor out of which he selects 19 cases which gave unusual findings. The spinal fluids were analyzed from the standpoint of cell count, Lange's gold curve, the Nonne test and the Wassermann reaction. He found a high cell count in all of these 19 cases (8 to 679 cells, with a count most commonly between 14 to 20 per cubic millimeter). Of the whole series, 41 fluids were negative. He does not state what the picture was in the remaining 67 cases.

Mouriz,[4] from the analysis of spinal fluids from 8 cases of brain tumor, concludes that the most important details in the spinal fluid are an increase in total protein with a low cell count, and a characteristic gold curve. He also states that xanthochromia, when present, is a most important sign.

About one year prior to the present investigation a series of cerebrospinal fluids, chiefly obtained by ventricular puncture during the course of operation from cases suspected of brain tumor in Dr. Cushing's clinic, were examined by Dr. B. J. Alpers. The results obtained were sufficiently suggestive to warrant a continuation of the investigation. Our study was therefore undertaken with the hope of establishing a sufficiently definite picture in lumbar and ventricular fluids from cases of tumors of the central nervous system to be of service in arriving at a diagnosis. An attempt was made to diagnose each case from the picture presented by the cerebrospinal fluid itself. This diagnosis was then checked up with the clinical evidence, and with operative and autopsy findings when such were available. In the final analysis of the data presented, certain uniform standards were established. It is not to be supposed, however, that the standards are fixed, for, as additional data are accumulated, they will, no doubt, be modified to fit new facts. Emphasis is therefore to be placed on the preliminary nature of this report, in which the exact pathological nature and position of the lesions, whether subcortical, submeningeal or subependymal, are not taken into consideration.

It should be mentioned that the spinal fluids in cases of brain tumor have been secured only as a result of cautious preoperative

tests, such as in the making of ventriculograms, etc. The majority of the fluids have been secured during the course of operative procedures. The predominant number of ventricular fluids and of subtentorial lesions is due to the fact that ventricular puncture is a routine step in the course of the majority of operations for tumors in this situation.

II. Methods

The cerebrospinal fluids were examined in accordance with the following scheme:

1. General Appearance and Physical Characteristics. Here clarity, colorlessness, turbidity of varying degrees, due either to cellular elements or bacterial contamination, and xanthochromia were noted. In order to quantitate the degree of xanthochromia present, a modification of the Bernheim Icterus Index[5] method was used. A series of tubes, containing solutions of known concentrations of potassium dichromate, ranging from a dilution of 1:100 to 1:200,000, was employed. The xanthochromic fluid was then matched in a comparator against the colors of the standards, and the xanthochromia designated numerically. As in the Bernheim scale, the 1:10,000 potassium dichromate solution was regarded as unity. The number of any other dilution was obtained by making use of the simple mathematical expedient below:

$$1 \times 10{,}000 = \text{No. of dilution} \times \text{dilution figure}$$

To illustrate:

$$1 \times 10{,}000 = 100 \times X$$
$$X = 100$$

Hence a dilution of 1:100 potassium dichromate solution would be placed at 100 on the scale. The xanthochromic index in the cerebrospinal fluid in the cases studied rarely exceeded one. Xanthochromic indices are hence usually expressed by fractional numbers.

2. Cellular Content. A determination of the number of red blood corpuscles was made on each fluid examined, even though there was no macroscopical evidence of contamination with blood.

White cell and differential counts were made following the technique of Levinson.[6] The diluting fluid was made according to the following formula:

Methyl violet	0.1 gm.
Glacial acetic acid	2.5 c.c.
Distilled water	50.0 c.c.

An ordinary white counting pipette was used. The diluting fluid was drawn up to the figure 1, and the pipette filled with spinal fluid to the figure 11, shaken thoroughly and allowed to stand for ten minutes to insure proper staining of the white cells and hemolysis of the red cells. A drop of the mixture was placed on a Levy counting chamber (Neubauer ruling) and a determination of the number of white cells made by taking into account the dilution of the fluid and the correction for the counting chamber. With this stain the nuclei of the white cells stand out clearly, thus making it quite easy to make a differential count in the fresh specimen. In using a staining fluid such as this it

is quite desirable to place in a separate chamber the sample of fluid to be counted, else the whole supply may become discolored with the dye, thereby obscuring the presence of xanthochromia. The customary procedure was to place about 1 c.c. of the fluid in a small test tube and from this to make a red and white cell count, using the remainder for a qualitative globulin determination. Thus the original sample arrived at the chemical laboratory uncontaminated.

3. GLOBULIN; QUALITATIVE AND QUANTITATIVE. These determinations were made according to the Nonne-Apelt[7] reaction (Phase 1). The results were consistently read against a black background after the lapse of one minute. They were interpreted as follows:

1. Indistinct ring, $\pm$
2. Distinct ring, $+$
3. Heavy ring, $++$

An attempt was made in the earlier part of the problem to establish a quantitative method for the estimation of the globulin fraction of the protein content of the cerebrospinal fluid. A nephelometric method given by Pfeiffer, Kober and Field[8] was used, but was abandoned because of its very decided limitations in ventricular fluids containing minimal amounts of protein, and because it required large quantities of fluid. The results obtained in the few fluids examined pointed to a rather constant 1:3 ratio between the globulin and total protein, thus indicating either that a quantitative estimation of the globulin fraction is of no advantage over a qualitative estimation of the total protein value, or that the method lacked accuracy and delicacy.

4. TOTAL PROTEIN. Emphasis was placed on the estimation of the total protein in the cerebrospinal fluid. A modification of the Denis and Ayer[9] method was used. A brief exposition of this method is here given: To 1 c.c. of spinal fluid, or 2 c.c. of ventricular fluid, an equal quantity of 23 per cent sulphosalicylic acid is added, and the mixture shaken. The spinal fluid is further diluted by the addition of 10 c.c. of distilled water. The clouds thus produced are read in the nephelometer against a protein standard (45 mgms. per 100 c.c. of fluid) which is precipitated and diluted in the same way as the spinal fluid. Since the relationship of

$$\frac{\text{Reading of known}}{\text{Reading of unknown}} = \frac{\text{Protein concentration of known}}{\text{Protein concentration of unknown}}$$

obtains only within narrow limits, it was found necessary to correct the calculated values on the basis of a curve obtained experimentally by plotting actual protein concentrations against nephelometer readings. The variations from calculated values, in the more concentrated protein solutions (i.e., 110 mgms. and above) reached a value of 30 per cent and over of these calculated values. Even with such a safeguard it was found advisable to discard results that gave readings below 13 or 14 when the standard was set at 20. Two methods were used for bringing fluids containing high protein values within the limits assigned: the one indicated by Denis and Ayer in their original paper, diluting the spinal fluid with water previous to precipitation; the other, diluting the fluid with water after precipitation, and thus exceeding in amount the allotted 10 cubic centimeters.

5. Lange's Colloidal Gold Curve. This test was made on every fluid examined. The gold reagent was prepared according to Stitt's newest method,[10] which differs from previous methods in its omission of oxalic acid, and its use of a redistilled formalin. Freshly distilled water (once distilled and occasionally double distilled) was used instead of the traditional triple distilled. The reagent was standardized against fluids known to give one of the following characteristic reactions: (1) the negative fluid; (2) the fluid with the strong paretic curve and (3) the fluid with a well-defined luetic curve.

Curves obtained were placed in the following categories (the classification adopted by The Peter Bent Brigham Hospital):

a. Type I, the luetic curve, interpreted as positive or doubtful (1223100000).

b. Type II, the paretic curve, interpreted as positive or doubtful (5555554310).

c. Type III, the curve characteristic of brain tumor and tuberculous meningitis, interpreted as positive or doubtful (0000123100).

d. Type IV, the curve characteristic of meningitis other than tuberculous, interpreted as positive or doubtful (0000012334).

6. The Wassermann Reaction. A routine test was made on each fluid. Dilutions varying in amount from 2 c.c. to 0.1 c.c. were employed.

7. The Sugar Content. Sugar determinations were made routinely on every fluid examined. The method of Folin and Wu[11] was followed. Use was made of the protein free spinal fluid filtrate, rather than of the spinal fluid itself (Alpers, Campbell and Prentiss[12]), since the material on hand included spinal fluids with so wide a variation in protein content. A dextrose standard equivalent to 75 mgms. per 100 c.c. of fluid was found most serviceable.

III. The Normal Cerebrospinal Fluid

In order to establish a norm for the laboratory values of fluids in cases of tumor of the central nervous system, it is first necessary to define the cellular, chemical and serological relationships obtaining in normal cerebrospinal fluids. It is scarcely necessary to state that the normal fluid, particularly the ventricular fluid, is rarely found in our laboratories. Hence the laboratory worker finds it imperative to fix some more or less arbitrary standard for a basis of comparison. The normal values cited below were derived by averaging the results obtained from three distinct groups. Group I included proved negative cases which were negative serologically. (The term "negative serologically" as used in this paper means negative from the standpoint of all tests listed under the methods given.) Group II included proved cases of arachnoiditis that were negative serologically. Group III included unproved cases negative serologically. In ventricular fluids an additional group, Group IV, composed of proved brain tumor cases, negative serologically, was used.

The normal spinal fluid, as established in the manner outlined above, showed the following characteristics:

1. It was clear and colorless.

2. The white cell count varied from 0 to 8 cells, with an average count of 2 to 3 cells. These cells were mononuclears.

3. The globulin was negative by Phase I of the Nonne-Apelt reaction.

4. The total protein value varied from 21 to 47 mgms. per 100 c.c. of fluid, with an average value of 37 mgms. per 100 c.c. of fluid.

5. The gold curve was negative.

6. The sugar content varied from 57 to 84 mgms. per 100 c.c. of fluid, with an average of 74 mgms. per 100 c.c. of fluid.

7. The Wassermann reaction was negative.

The normal ventricular fluid gave a picture that varied markedly only in one respect from that presented by the normal spinal fluid. This was in its protein value, which ranged from 5 to 18 mgms. per 100 c.c., and averaged 7.8 mgms. per 100 c.c. The sugar content showed more constancy in quantity, 61 mgms. per 100 c.c. being a low normal, 79 mgms. per 100 c.c. a high normal and 73 mgms. per 100 c.c. the average value. From a large number of spinal fluids of medical cases submitted to the laboratory, on which sugar values were obtained, but which could not be classed as serologically negative because of insufficient data, the information was gained that the average sugar value of the spinal fluid was somewhat lower than that of the ventricular fluid, and that this average value was 69 mgms. per 100 c.c. of fluid.

IV. The Fluids in Cases of Tumor: Spinal and Cerebral

In spinal fluids the findings varied markedly, depending upon the location of the tumor.

Spinal Cord Tumor with Block in the Cerebrospinal Fluid Circulation. All but one of the cases studied presented the typical Froin syndrome; hence they were associated with some sort of block. The spinal fluid under these conditions presented the following characteristics:

1. It was xanthochromic and frequently clotted on standing.

2. The cell count was low, usually under three.

3. The globulin was markedly positive.

4. The total protein value averaged 3600 mgms. per 100 c.c. of fluid.

5. The gold curve varied with the amount of protein present. Generally speaking, a total protein value below 1000 gave a positive Type III curve; between 1000 and 2000 a doubtful Type IV curve, and above 2000 a positive Type IV curve. In passing, it may be said here that the type of gold curve produced seems to be dependent upon the quantity of protein present. Only in so far as protein values overlap in fluids producing gold curves of Types I and II, can the gold reagent be said to possess a qualitative differentiating power.

6. The sugar value showed no significant change.

7. The Wassermann was negative.

Spinal Cord Tumor without Block. Here the findings were intermediate between those of spinal cord tumors with block and brain tumor.

Spinal Fluid in Brain Tumor. The fluid presented the following characteristics: (1) It was usually clear and colorless or slightly xanthochromic; (2) the cell count was low, usually under three per cubic millimeter; (3) the globulin was positive; (4) the total protein value most frequently lay between 250 to 300 mgms. per 100 c.c.; (5) the gold curve fell in the Type III category; (6) the sugar content did not vary appreciably, and (7) the Wassermann was negative.

Ventricular Fluid in Brain Tumors. In this fluid the variation was in the same direction as in the spinal cases; that is, an elevation of the total protein, with the type of gold curve corresponding to that elevation. These fluids showed a normal protein content; that is, ⅓ to ¼ that of spinal fluids. This fact markedly influences the abnormal picture obtained.

A statement of the conditions in ventricular fluids positive for brain tumor would include the following items:

1. The fluid was clear and colorless, rarely showing a xanthochromia.

2. As in the spinal fluid, the cell count was generally below three per cubic millimeter.

3. The globulin was usually doubtfully positive.

4. The total protein value in the cases studied varied from 23 to 132 mgms., with an average of 52 mgms. per 100 c.c. of fluid.

5. The gold curve fell in the Type I group, occasionally approaching the Type II group.

6. The sugar content did not vary significantly.

7. The Wassermann was negative.

V. Presentation of Data

Fluids from 108 patients were examined. The diagnosis in 65 cases was verified either by operation or autopsy, and in 4 cases by well-established and generally accepted laboratory methods. These four cases include 3 of cerebrospinal syphilis and one of tuberculous meningitis, in which latter case the spinal fluid gave a positive inoculation test for the tubercle bacillus.

All bloody fluids were discarded. One fluid in the series showed a red cell count of 700, and the rest were either negative for red

blood cells or gave counts below 85. As to the justification for including the fluid with the erythrocyte content of 700, it may be said in passing that work done in this laboratory on the effect of the red blood cell content upon the total protein value and on the gold curve would indicate that only when the red blood cells exceed 2000 per cu. mm. is a demonstrable change produced.[13] Fluids were excluded when information on either a cell count or a sugar content was lacking, since one or the other of these was regarded as necessary for distinguishing between fluids presenting the picture of inflammation and those presenting the picture of tumor.

Of the 68 proved cases in which an attempt was made to determine the diagnosis on serological data alone, 48 (71 per cent) were diagnosed correctly, 11 incorrectly (16 per cent), and 9 were listed as questionable (13 per cent). The questionable group includes those cases where some portion of the data showed a variation from what was considered to be the typical picture.

There were in all 39 proved cases of tumors of the central nervous system. From this group fluids were obtained from the lumbar region in twelve instances, and from the ventricles in twenty-seven instances. Of the twelve spinal fluids examined, the location of the lesions was distributed as follows: spinal, 4; supratentorial, 4; subtentorial, 3, and suprasellar, 1.

Of the 27 ventricular fluids examined, the lesions were found to be as follows: subtentorial, 17; supratentorial, 7, and suprasellar, 3.

A correct serological diagnosis of tumor was made in 75 per cent of the spinal fluids examined, incorrect diagnosis in 8 per cent, and 17 per cent were listed as questionable. Of the twenty-four ventricular fluids examined, 48 per cent were diagnosed correctly, 26 per cent incorrectly and 26 per cent as questionable.

In analyzing the incorrect diagnoses, we find that the one mistake made in the spinal fluid group occurred in a case of a cerebellar glioma. The seven errors made in the ventricular fluid group occurred in tumors of the posterior fossa. This consistency is quite striking. One cannot help wondering what the fluid from the cisterna magna would have shown in these cases. It seems logical to suppose that the cisternal fluid would be most likely to give a tumor picture in lesions of the posterior fossa. Unfortunately we have no laboratory data at present on fluids obtained by cisternal puncture, though it has often been remarked that the cisternal fluid encountered at operation in acoustic tumor cases

is grossly xanthochromic, while the ventricular fluid from the same case is colorless.

In the list of proved cases there were 13 instances of chronic arachnoiditis which were represented by five lumbar fluids and eight ventricular fluids. A negative spinal fluid, in the presence of symptoms simulating brain tumor, led to a diagnosis of chronic arachnoiditis which was proved to be correct in all the cases in which the spinal fluid was examined, and in all but two from which ventricular fluid was obtained. We have found no variations in the chemical content of the cerebrospinal fluids from these cases. There appears, however, to be a tendency toward a slight increase in the white cell count; i.e., an average of seven white blood cells per cubic millimeter (all mononuclears).

It is of importance to note that all of the proved negative cases gave negative laboratory findings. Thus far the errors have all been in making negative serological diagnoses when a tumor was present rather than in making positive diagnoses when no tumor was found. This seems to be of considerable practical importance as one may feel sure that there is a lesion present when the value of the various components of the cerebrospinal fluid is definitely above a high normal level.

Just what mechanism is responsible for the changes observed in the cerebrospinal fluids in cases of tumor is problematical. We believe that the greater part of the picture is probably due to an increase in protein caused by an exudation around the tumor; therefore, the larger the tumor mass and the more intimate contact it has with the cerebrospinal space, the more marked the chemical variations in the fluid will be.

Summary

1. The normal ventricular fluid differs markedly from the normal spinal (subarachnoid) fluid in only one respect; namely, in its total protein content, which is one-third or one-fourth as great as in the spinal fluid.

2. The picture presented by the spinal fluid in brain tumor is marked by a low cell count, a high total protein value, a characteristic gold curve (Type III) and no significant variation in the sugar content.

3. The changes in the ventricular fluid are in the same direction as in the spinal fluid. The significant points are, therefore, an ele-

vation in the total protein content above the normal, and a gold curve characteristic of that total protein value (Type 1). A low cell count and a normal sugar content accompany the picture.

4. In chronic arachnoiditis both spinal and ventricular fluids consistently show no deviations from the normal.

5. All fluids from cases in which no lesion was found gave negative laboratory findings. Positive results therefore indicate the presence of some pathological lesion, although occasional negative results as in the case of chronic arachnoiditis do not exclude a pathological process.

6. A larger incidence of correct diagnoses occurred in the study of the spinal fluids (75 per cent) than in that of the ventricular fluids (42 per cent).

7. The analysis of fluids grossly contaminated with blood is of no value. Whenever the red cell count approximates 2000 cells per cubic millimeter, the value of the analysis is questionable; if the total protein content and gold curve are such as not to be accounted for by the contaminating blood, it is safe to assume that some lesion is present.

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Chapter XXVI

THE LEVINSON TEST AND OTHER LABORATORY STUDIES IN TUBERCULOUS MENINGITIS*

C. A. PONS, M.D., AND THELMA A. FLETCHER

THE typical cerebrospinal fluid in tuberculous meningitis is usually clear or slightly turbid, increased in amount and under pressure. The globulin is increased, there is a moderate increase in the leucocytes with the small lymphocytes greatly predominating, and the sugar content is within normal limits. These findings do not per se confirm the diagnosis of tuberculous meningitis, nor do they exclude other possibilities, such as cerebrospinal lues, paresis, encephalitis, poliomyelitis, etc. Further than this, cases of tuberculous meningitis have been reported in which the predominating cell was the polymorphonuclear leucocyte; hence in these rare cases we meet the possibility of confusing the condition with a purulent meningitis, providing the bacteriological examination is negative, as sometimes happens, especially in epidemic meningitis.

There are various tests that help in differentiating some of the conditions resembling tuberculous meningitis; for example, the negative Wassermann reaction and colloidal gold curve usually rule out an active lues. But these are time-consuming and difficult except for the experienced worker and, moreover, are often not available.

The crucial test in proving that the fluid in question is tuberculous is, of course, the finding of the acid-fast organism. This is not an easy task and frequently unsuccessful, and, although, as a last resort, a guinea-pig inoculation can be made, the report is necessarily delayed five to six weeks.

Various procedures have been suggested for finding tubercle bacilli: allowing the fluid to stand undisturbed over night in an incubator is supposed by some to increase the number of organisms, while others advise the addition of an equal volume of 95 per

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cent alcohol when there is no pellicle. While the pellicle is often present in tuberculous spinal fluids, many have the impression that it is found only in tuberculosis. This impression should be corrected, as pellicles have occurred in other conditions. When, however, a pellicle does form, the probabilities of finding the bacillus are increased.

Of the various chemical tests that have been suggested, the precipitation test of Levinson[1] has been found to be extremely valuable. Proteins are precipitated as albuminates when treated with certain metallic salts, such as copper sulphate, zinc chloride, bichloride of mercury, and so forth, and precipitated as insoluble salts when treated with weak organic acids, such as certain of the alkaloidal reagents, picric, phosphotungstic, tannic and sulphosalicylic acids.

Levinson claims that in cases of suppurative meningitis the sulphosalicylic acid throws down a precipitate, the height of which in millimeters is three times as great as that thrown down by the mercuric chloride; whereas in tuberculous meningitis the reverse is the case, i.e., the bichloride precipitate is twice that of the sulphosalicylic acid.

While the protein content of the fluid in cerebrospinal meningitis is usually greater than in tuberculous meningitis, the range according to Mestrezat[2] being 0.15 per cent to 0.85 per cent for epidemic meningitis and 0.13 per cent to 0.56 per cent for tuberculous meningitis, Tashiro and Levinson[3] concluded, after carefully conducted experiments, that the test did not depend on the relative amounts of protein present, but on the hydrogen-ion concentration.

The changes in the hydrogen-ion concentration of the fluids on standing were investigated and a difference was noted, which was in itself sufficient to alter the electrical charges of the proteins. It was found that in epidemic meningitis most of the proteins are positively charged, while in tuberculous meningitis the negatively charged proteins predominate; hence the more positively charged proteins present in epidemic meningitis give a higher precipitate with the sulphosalicylic acid which is negatively charged, than with the bichloride of mercury which is positively charged, the reverse being the case in tuberculous spinal fluid.

Various alkaloidal metallic precipitants have been used, but the results at best only equal those obtained with the two reagents proposed by Levinson. Various dilutions of the spinal fluid, and various strengths of the reagents have also been utilized. In very

cloudy spinal fluids it may be advisable to use various dilutions of the spinal fluid. The merits of the stronger solutions, along with the original test as proposed by Levinson, will be given at length.

A study of tuberculous meningitis was undertaken with this test in view. It was found that in a number of cases in which the presence of the tubercle bacilli in the spinal fluid was established, either before death or at autopsy, the one to two ratio of the two precipitates held good in practically all of the cases; furthermore, in most of the cases, this one to two ratio was obtained before the finding of the bacillus.

Routine Observed in Testing the Cerebrospinal Fluid

The following routine was observed: The spinal fluid was received in two sterile test tubes; one was used for a differential cell count and one for the precipitation test. In performing this test Levinson's technique was followed at first. Small test tubes of about 8 mm. in diameter were used. One c.c. of spinal fluid was placed in each of two tubes. To one was added 1 c.c. of a 1 per cent mercuric chloride solution and to the second 1 c.c. of a 3 per cent sulphosalicylic acid solution. The tubes were shaken well, stoppered and allowed to stand at room temperature for twenty-four hours. At the end of that time the column of precipitate was measured in millimeters. The second tube of spinal fluid was left undisturbed until a pellicle had formed. This usually took place in less than twelve to fourteen hours. The pellicle was then fished out, teased out well and stained for tubercle bacilli in the routine manner. When no pellicle was formed, the fluid was centrifuged at high speed for half an hour. This sometimes forms a small pellicle; or else by the addition of 95 per cent alcohol, the proteins can be precipitated and on centrifuging a compact sediment results. Occasionally, guinea-pig inoculation was resorted to.

The two precipitates are of an entirely different character: that of the sulphosalicylic acid is heavy and compact and starts to form immediately, while that of the mercuric chloride is light, feathery and forms slowly. Sometimes the precipitate does not come down into a compact sediment, as small floccules may become adherent to the walls of the test tube. It was found advisable gently to shake the tubes two to three hours before making the final reading. If it is remembered that it is not the amount of protein thrown down in the two precipitates, but the relative height of the column of protein in millimeters in each tube, the results are more uniform.

Another difficulty encountered was that in some cases a precipitate was not obtained and the fluid remained cloudy. It was thought that, in these cases, either lower dilutions of the fluid, or stronger reagents would avoid this difficulty. Better results were obtained by the use of stronger reagents; and consequently 1 per cent and 2 per cent bichloride and 3 per cent and 6 per cent sulphosalicylic acid solutions were used.

With reference to the use of these higher strengths an analogy with the use of the cholesterin antigen in the Wassermann reaction seems permissible. The use of the cholesterin antigen alone would no doubt increase the number of false positive reactions, as well as the strength of the positive test, yet no serologist at present would do without it and as a rule a less sensitive antigen is also used. The use of the stronger solutions in this test is valuable in border-line cases and especially where the lower solutions fail to bring down a sediment.

Cases Showing a Positive Levinson Test

J. R., adult male, admitted to the Psychopathic Wards of the Philadelphia General Hospital. The provisional diagnosis was epidemic encephalitis. Study of the cerebrospinal fluid showed 217 cells per cubic millimeter, of which 4 per cent were polymorphonuclears and 96 per cent lymphocytes. No organisms were found on smear or culture. The Wassermann and the colloidal gold excluded syphilis of the nervous system. The Levinson test gave a precipitate of 3 mm. with sulphosalicylic acid and 9 mm. with bichloride, a ratio of 1:3. Because of this, a guinea pig was injected and five weeks later the animal was autopsied. Typical lesions were found and tubercle bacilli recovered. The patient was removed to the Jewish Hospital of Philadelphia, and there the organism was found in the spinal fluid. This case illustrates the diagnostic value of the test. It is unfortunate that we have not obtained any fluids from cases of epidemic encephalitis.

J. L., adult male, admitted to the Men's Tuberculous Wards of the Philadelphia General Hospital with definite symptoms of pulmonary tuberculosis. Later the patient developed symptoms and signs of meningitis. With the first lumbar puncture fluid the Levinson test was indicative of tuberculous meningitis, but no organisms were found. Three days later, another puncture was performed; the Levinson ratio was then 1:3.4, and we were successful in finding the tubercle bacilli.

This last case illustrates a not uncommon experience; namely, that the Levinson test is generally positive before the organism can be found.

R. W., adult male. This patient was admitted to the Medical Wards of the Philadelphia General Hospital with tuberculous cervical adenitis and symptoms and signs suggestive of meningitis. This case is reported because of the interesting cytology, (Table XLVI).

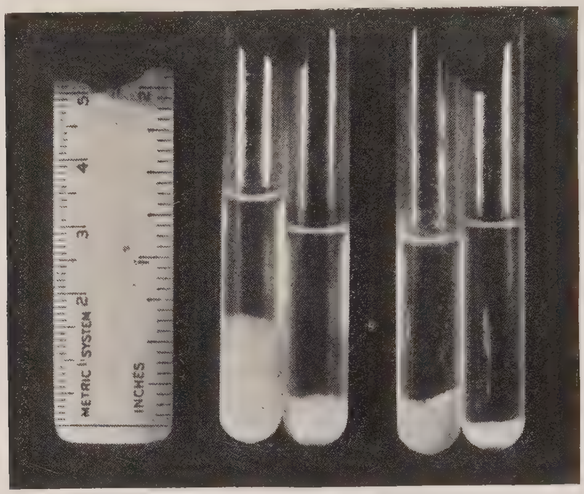

Fig. 68. Precipitates formed in mercuric chloride and sulphosalicylic acid solutions. Right to left: (1) Mercuric chloride. (2) Sulphosalicylic acid, three days before death. Ratio, 1:3. Tuberculosis found. (3) Mercuric chloride. (4) Sulphosalicylic acid, one week before death. Ratio, 1:2. No tuberculosis found.

Table xlvi

Cytology in Case of Tuberculous Cervical Adenitis and Meningitis

Count	Cell count	Polymorphonuclears, per cent	Lymphocytes	Ratio, old sol.	Ratio new sol.	Tubercle bacilli
1	1350	75	25	1:2.5	1:2.9	—
2	56*	29	69	1:1.75	1:2.5	+
3	430	25	75	1:2.5	1:2.8	—

* Pellicle present.

In this case the first spinal fluid showed 75 per cent polymorphonuclears, and at this time the case might have been considered a purulent meningitis; yet the ratio, sulphosalicylic acid to bichloride, was 1:2.9, suggesting tuberculous meningitis. On the next count the polymorphonuclears were diminished to 25 per cent. Another case, E. G., showed 46 per cent polymorphonuclears, 46 per cent lymphocytes and 8 per cent endothelial cells. This high proportion of polymorphonuclears sometimes occurs in tuberculous meningitis.

Conclusions

Results obtained with the Levinson test were consistent, with one exception, in the 20 cases of tuberculous meningitis reported. The ratio was 1:2 or above.

Furthermore, by using this test, the search for tubercle bacilli is encouraged, and since success in finding the organism is almost in direct proportion to the efforts of the examiner, the test, in this sense, is also valuable.

The 1:2 ratio was often established before the finding of the organism; while in other cases in which the organism was not found, the fluid was injected into a guinea pig, or post-mortem findings supplied the necessary confirmation.

In 3 cases in which the tentative clinical diagnosis was not tuberculous meningitis, because of the results obtained with the precipitation test, either smears were made or the fluid was injected into a guinea pig, and thus independently of any clinical knowledge the diagnosis of tuberculous meningitis was made.

Before the stronger solutions were used, several cases came to observation in which, because no precipitate was obtained in the 1 per cent bichloride, further investigations to prove the cases of tuberculous meningitis were discontinued. These cases were, of course, not included in this study. We believe that, with the stronger solutions, this difficulty will be avoided and results will be more uniform.

Unfortunately, the 1:2 ratio is not pathognomonic of tuberculous meningitis, as 6 cases of cerebrospinal syphilis out of 24 studied (25 per cent) gave a ratio of 1:2 or over. If, however, a ratio above 1:2 is considered as usual in tuberculous meningitis, which, in the light of this investigation, seems permissible, the value of the precipitation test in differentiating between cerebrospinal syphilis and tuberculous meningitis is increased.

No definite conclusions can be drawn as to the behavior of the test in miscellaneous conditions, as the number of cases were not sufficient to warrant such conclusions. Almost uniformly a higher precipitate was obtained with sulphosalicylic acid than with the bichloride solution.

Summary

1. Levinson's observation that the height of the precipitate in the bichloride of mercury solution is twice that of the sulphosalicylic precipitate is confirmed.

2. A 1:2 ratio is very suggestive, but not pathognomonic of tuberculous meningitis.

3. The use of stronger reagents, together with those proposed by Levinson, is suggested as increasing the diagnostic value of the test.

The test should be performed in every case of meningitis, because it is (*a*) easy to do; (*b*) because it is inexpensive, and (*c*) because it gives valuable diagnostic information.

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SECTION VI

THE REACTION OF THE HUMAN CEREBROSPINAL FLUID IN EXTRANEURAL DISEASES

Section VI

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Chapter XXVII

THE HUMAN CEREBROSPINAL FLUID IN GENERAL SYSTEMIC AND METABOLIC DISEASES, AS IN NEPHRITIS, DIABETES, ETC.

BERNARD J. ALPERS, M.D.

SO little has been written, and so little is generally known about the spinal fluid in such conditions as diabetes mellitus, nephritis, jaundice, gout and other similar conditions, that a review of the results of examinations of the cerebrospinal fluid in these conditions is not without value. The cerebrospinal fluid has been more thoroughly studied in other diseases mainly because such examinations are often necessary to establish or corroborate the diagnosis. In the diseases with which this paper deals, spinal fluid investigations are probably not an indispensable aid in diagnosis, but in certain of the conditions they are of distinct value in determining the diagnosis and prognosis; and, indeed, the determination of the findings which occur in these conditions may be of value as an approach to further physiological studies on the cerebrospinal fluid.

Diabetes

According to Mestrezat,[1] there are two features of importance in the spinal fluid of diabetes; one is the presence of sugar in abnormal proportions, and the other is the presence of acetone. In all other respects, viz., in the number of cells, in the pressure, the albumin and the gold curve, the spinal fluid is essentially normal. The basis for the study of the spinal fluid in diabetes mellitus is provided by nineteen spinal fluids from various hospitals in the

city of New York. An analysis of these 19 cases shows the cell count to vary from 1 to 7 cells per cubic millimeter in 11, or 60 per cent, of the cases, and from 10 to 28 in 8, or 40 per cent, of the cases, 5 of these showing a count of 20 or more cells per cubic millimeter. In most of the cases in which the cell count was increased, a complication of some sort was present, such as a neuritis, gangrene, bronchopneumonia, pulmonary tuberculosis or a cerebral vascular lesion. In all of the cases except one the spinal fluid pressure was normal, being definitely increased in one case. The protein content was not increased in 10 cases, while in 9 cases it was increased but slightly. In one instance a protein content of 90 mgms. per 100 c.c. was found. In only one of the 19 cases was a quantitative sugar estimation made, in which case a sugar content of 175 mgms. per 100 c.c. was found. The Wassermann reaction was negative in all of the cases. In 4 instances the colloidal gold curve showed a reduction in the lower dilutions.

All writers agree that the sugar in the spinal fluid is increased in diabetes, but the amount of increase is not a matter of unanimity of opinion. The sugar may be increased in amounts varying from 0.3 to 3 per cent, but may be even as high as 5 to 6 per cent. Acetone is usually present, some authors reporting it early in the disease, and some stating that acetone appears only in coma or immediately before coma. Diacetic acid has been found in only a few instances, and then only in coma. Bousquet and Derrien[2] report 2 cases of diabetes with acetone in the urine and spinal fluid before coma, and 3 cases in which acetone was found in the spinal fluid before it appeared in the urine. They contend, therefore, that the spinal fluid findings in diabetes may be of some value in the determination of an impending coma in cases where no evidence of acidosis is present in the urine. Erben[3] also states that there may be acetone in the spinal fluid without an acetonuria. He found acetone in a series of comatose diabetics, in amounts as high as were determined in the urine. He has established that the spinal fluid examination is of importance in those patients who are admitted to a hospital in a comatose state, and from whom no urine is obtainable.

Mestrezat[1] states that before coma the sugar is increased from 0.9 per cent to 2.7 per cent and that in coma the sugar is very much increased, from 2.2 per cent to 5.5 per cent. He has determined that as the blood sugar returns to normal, the spinal fluid sugar declines pari passu. He believes that the presence of acetone is not pathognomonic of diabetes, but that in a spinal fluid with a

sugar over 0.9 per cent the presence of acetone confirms the diagnosis. He considers the acetone test as of importance in the differential diagnosis of coma. Frazier[4] found the presence of acetone a frequent forerunner of coma. Lochelongue[5] believes that acetone is present in large amounts in coma, but may be met before coma. Eskuchen[6] agrees with the latter determination, but Boyd[7] declares that acetone is never found in the fluid except in coma. He states that the increase in the spinal fluid sugar closely parallels that of the blood, and that cases of coma show the highest amounts of sugar. Diacetic acid is found more rarely than acetone, its presence being indicative of the extreme gravity of the condition. Boyd, too, lays stress on the value of the presence of acetone and sugar in the spinal fluid in a comatose patient from whom no urine can be obtained.

It may therefore be that the study of the spinal fluid in diabetes has more than an academic value, and that it may serve in the differential diagnosis of comatose states, and may even be of value in determining the prognosis of certain cases of diabetes. The statement may justifiably be made that, in those cases of diabetes with definite evidence of an inability to utilize sugar, with an increase in the sugar content of the blood and the presence of sugar in the urine, an increased sugar content will be found in the spinal fluid, but that the amount need not be proportional to the level of the blood sugar. In cases of impending coma and in cases with coma, acetone is usually present, and sometimes also diacetic acid. These substances are usually present in the severer stages of diabetes.

Nephritis

The spinal fluid constituents in nephritis vary with the presence or absence of uremia. In cases of chronic nephritis without uremia, the pressure is usually increased but may be normal, and the cells are usually normal in number and character. Forty-one spinal fluids from cases of chronic nephritis from various hospitals in New York were studied. The type of chronic nephritis was not always stated, but most of the spinal fluids were from cases of chronic nephritis with hypertension. All of the fluids were clear and colorless. In 34, or about 83 per cent, of the cases the cell count was normal, varying from 0 to 5 cells per cubic millimeter. In 7, or 17 per cent, of the cases the cell count was definitely increased: 4 of these cases presented from 9 to 19 cells per cubic

millimeter, and 3 cases showed counts of 50, 120 and 155 cells per cubic millimeter. In one of these cases the patient died with a pneumonia; in another a hemiplegia was present to complicate the nephritis, and in another Jacksonian epilepsy was present. No records of the pressure in this last condition were available. In 12, or about 30 per cent, of the cases there was a slight to moderate increase in the albumin and globulin content. In only 14 cases was a Wassermann reaction recorded, and in all these cases it was negative. Sugar was stated to be present but no quantitative figures were available.

In cases of chronic nephritis with edema, Mestrezat[1] says that there is a marked increase in the chlorides of the spinal fluid. Eskuchen,[6] Boyd[7] and Levinson[8] also state that the chlorides are increased in these cases, often to 0.8 or 0.85 per cent. The urea content in cases of chronic nephritis without uremia is about normal. Mestrezat[1] says it is usually below 0.1 per cent, but that in exceptional cases it may exceed this amount. Lochelongue[5] agrees with this statement, and places the urea content in chronic nephritis without uremia at 0.1 per cent to 2.2 per cent. Von Monakow[9] reports the presence of uric acid and creatinine in increased amounts in the spinal and ventricular fluids of a case of chronic nephritis.

The presence of uremia alters the spinal fluid formula. Mollard and Froment first used the classification of "pure" and "associated" uremia, and this classification has been accepted by the majority of writers on this subject. By the former is meant a uremia without known cause, while by the latter is meant a uremia secondary to some definite organic etiological factor. In a pure uremia the cells are occasionally increased (Mestrezat[1]). The pressure is increased almost constantly, and there is an increase in the chlorides, the urea content is elevated, and some authors report an increase in the sugar content, Lochelongue[5] stating that the more grave the uremia, the higher is the sugar content. While all writers agree that the urea content is increased in pure uremia, the figures vary with various writers. Mestrezat[1] gives 0.4 per cent to 2.55 per cent as the variations in the urea content in pure uremia; Canti gives from 0.098 per cent to 0.634 per cent, and Boyd[7] gives 0.1 per cent to 6 per cent. In any event, the urea is definitely increased.

In cases of "associated" uremia, the amount and pressure of the spinal fluid are increased and the cells are usually normal; but

there may be a lymphocytosis, the albumin is increased and the chloride values are reported to be definitely elevated. The urea content is very much increased. Canti[10] reports the urea content to be 0.1 per cent to 0.764 per cent and Levinson[8] states that the urea content may be as high as 55 mgms. per 100 c.c. Boyd[7] has determined urea to be present in amounts varying from 0.1 per cent to 0.6 per cent, while Eskuchen[6] and Lochelongue[5] have found values as high as 1 per cent to 2 per cent and even as high as 4 per cent. Lactic acid is usually found in large quantities in the spinal fluid from cases of eclampsia.

Soper and Granat[11] have drawn certain conclusions as to the prognosis in cases of uremia, based on the amount of urea in the spinal fluid. They determined that a urea content of more than 0.2 per cent indicates a severe uremia and a rapidly fatal termination, that a content between 0.1 per cent to 0.2 per cent means a rapidly fatal termination in most cases of nephritis, and that a urea content of 0.05 per cent to 0.1 per cent permits of no definite conclusions as to prognosis or diagnosis, but that such a content is suggestive of severe urea retention. Mollard and Froment, on the basis of 23 cases, conclude that a urea content of 0.4 per cent indicates a pure uremia, and foretells a rapidly fatal outcome. A urea content below 0.4 per cent did not permit of any definite conclusions. Froment, on the basis of 34 cases, arrived at the same decision, and also stated that in cases with less than 0.1 per cent of urea, the diagnosis of uremia could be rejected. Canti[10] holds that "every case in which a greatly increased quantity of urea has been found in the cerebrospinal fluid has proved fatal within a short period." In summary, the urea determinations may serve as a very definite means of establishing both the prognosis and diagnosis in cases of "pure" and "associated" uremia.

Icterus

Except for the inconstant presence of a yellow discoloration to the fluid, the spinal fluid in jaundice is usually normal. Magendie, in 1827, demonstrated that the spinal fluid in jaundice shows a more or less pronounced yellow color. The intensity of the coloration varies: occasionally it is very yellow, at times slightly xanthochromic, and it may be colorless. Authors differ on the incidence of this coloration, some reporting it in every case, and others in only 15 per cent of the cases.

Mestrezat[1] reports four fluids, three of which were yellow. It is certain that not every spinal fluid in jaundice is discolored, and that from the statistics at hand the incidence of the discoloration may be placed at from 20 per cent to 30 per cent, these figures varying, of course, with the intensity, duration and cause of the jaundice. Levinson[8] says that "the color of the fluid is deep yellow." Lochelongue,[5] however, asserts that the color is but slightly different from the normal, and that there is no parallel between the color of the fluid and the gravity of the clinical case. Bile is demonstrable in the spinal fluid in cases of jaundice with a yellow fluid, and Mestrezat[1] concludes that this coloration is due to urobilin. A decrease in chlorides has been reported in the spinal fluid in jaundice, and a few cases have been reported with an increased spinal fluid sugar content. The pressure, cell content and albumin are usually normal. One case of an acute catarrhal jaundice of two weeks' duration showed no discoloration and no bile in the spinal fluid.

Gastroenteritis

The cerebrospinal fluid from 69 cases of gastroenteritis was investigated. No striking abnormalities were noted. In 13 of the cases an increased cell count was found, usually varying from 20 to 50, but in one case reaching 210 cells per cubic millimeter. The cells were chiefly lymphocytes, but polymorphonuclear leucocytes were present in many of the cases. All of the fluids were clear, and none of them showed an increase in pressure. The albumin and globulin content was normal in practically every case. The colloidal gold and Wassermann reactions were not done with any degree of uniformity, so that no conclusions as to these tests are available. Qualitatively, sugar is present in every case, sometimes in amounts which would probably show an increase over the normal if quantitated.

Gout

Very few studies have been made on the spinal fluid in this condition. Charcot reports the presence of urates in a spinal fluid from a case of chronic gout, and Mestrezat[1] states that one of the manifestations of the gouty diathesis may be the presence of urates or of uric acid concretions in the meninges or spinal fluid.

Cardiac Disease

Chronic Endocarditis. Seventeen cases of endocarditis were studied. In 11 cases the disease process involved the aortic valves, and in 6 cases the mitral valves. In the patients with aortic disease, 3 were cases of aortic stenosis, and 8 were instances of aortitis or of aortic regurgitation. In 10 of the cases of aortic disease the cell count was normal, never rising higher than 5 cells per cubic millimeter. In one case which showed evidence of a general arteriosclerosis the cell count was 12 cells per cubic millimeter. In every case the globulin and albumin content was normal. The Wassermann reaction was negative in every case. No conclusions could be reached with regard to the colloidal gold reaction. Fehling's solution was reduced in every case. In the 6 cases of mitral endocarditis (mitral stenosis) the spinal fluid values were normal in every detail.

Chronic Myocarditis. Five cases of chronic myocarditis showed spinal fluid determinations with no variation from the normal.

Subacute Bacterial Endocarditis. Eleven cases of this disease showed a clear fluid in every case. In four instances the cell count was increased, while in 7 cases it was normal. In 5 cases the albumin and globulin content was moderately increased and in 6 cases it was normal. Fehling's solution was reduced in every case. No observations were made as to the colloidal gold or Wassermann reactions. The spinal fluid in this condition shows no typical findings, and in most respects may be said to be normal.

Tuberculosis

Thirty-two cases of tuberculosis were studied. Of these, 7 were cases of miliary tuberculosis, 23 were cases of chronic pulmonary tuberculosis and 2 were cases of tuberculosis of the peritoneum and fallopian tubes. All the fluids save one were clear and colorless, the one exception being amber in color. Sixteen fluids, or 50 per cent, had a normal cell count. In 16 others, or 50 per cent, there was a definitely increased cell count ranging from 10 to 400 per cubic millimeter. The average level of the increase varied from 20 to 40 cells per cubic millimeter. In 7 cases the albumin and globulin content was slightly increased, but in all the other cases these constituents were normal. Cultures in 15 fluids were negative. No conclusions could be drawn concerning the Wassermann and colloidal gold reactions.

Malta Fever

The spinal fluid in this condition is normal. Lochelongue states that the sugar is always increased, and that a lymphocytosis is usual after infection of the subarachnoid cavity. In all other respects there is no deviation from the normal.

Endocrine Disturbances

Very few studies have been made on the spinal fluid in these disorders. Three cases of hyperthyroidism showed a normal cerebrospinal fluid. One case of hypothyroidism and one case of hypopituitarism showed no abnormalities. Bousquet and Derrien report the presence of acetone in the spinal fluid in the terminal stage of a case of Addison's disease. A case of acromegaly reported by Mestrezat shows a normal spinal fluid. Two of our cases of acromegaly showed interesting findings. In one case everything was normal save the protein and sugar findings, which were 61 and 130 mgms., per 100 c.c., respectively. Two examinations of another acromegalic fluid showed a xanthochromia on both occasions, 5 to 6 cells per cubic millimeter, a quantitative protein of 313 and 475 mgms., and a sugar content of 200 and 222 mgms. per 100 c.c. This case, however, was complicated by diabetes.

Toxic Conditions

Acute Alcoholic Intoxication. In this condition the amount and pressure of the spinal fluid are increased. Alcohol can be recovered in the spinal fluid, the amount varying from 1.5 per cent to 4 per cent, which is higher than the alcoholic content of the blood. There is a slight increase in the albumin content. The cell content is usually normal, but Levinson reports an occasional count as high as 26 cells per cubic millimeter. The chloride and sugar content is normal.

Chronic Alcoholism. The spinal fluid is normal in this condition.

Delirium Tremens. Diacetic acid and acetone have been reported in a few instances of this condition, but in all other respects the fluid is normal. Alcohol is not present unless it has been ingested within twenty-four hours before the fluid is taken.

Lead Poisoning. In cases which have an involvement of the meninges the spinal fluid pressure is increased to 400 or 500 mm. of water. The amount of fluid is increased, and there is usually a

lymphocytosis, the cells numbering from 50 to 250 per cubic millimeter. Lead is often found in the spinal fluid in these cases.

Miscellaneous Conditions

Myeloid Leucemia. Barker reports one case of myeloid leucemia in which the cell count was 267 per cubic millimeter. The cells were neutrophilic myelocytes and perhaps also myeloblasts. The globulin was slightly increased, but in other respects the fluid was normal. He reports also three instances from the literature, but none showed the presence of myelocytes. Bassoe reported a case which showed a normal spinal fluid. Topie and Cassar and also Munro reported cases with a normal spinal fluid.

Osteomalacia. Barker and Clough punctured a case with osteomalacia, but found no abnormal findings save a slight change in the mastic reaction (2210000000), and a spinal fluid sugar of 0.76 per cent.

Discussion

The following questions submitted to Dr. Alpers before the Commission, together with the answers to them, are here reported verbatim.

Dr. Gibbs: Does Dr. Alpers know of any observations on the pressure, sugar or other chemical components of the fluid in diabetes after insulin, especially in relation to convulsions?

Dr. Alpers: No, sir, I do not.

Dr. Sachs: I should like to ask Dr. Alpers just one question. I wish to say first that I fully appreciate the importance of all these investigations and it is well that the ground has been covered in that way, but would Dr. Alpers consider lumbar punctures a procedure that he would recommend in cases of diabetes without coma? Of course, in cases of diabetic coma, we could understand the reason perhaps for this procedure, but would he see the advantage of doing a lumbar puncture in the average case of diabetes?

Dr. Alpers: No, I believe that these reports are of chief importance from a physiological point of view rather than from the clinical point of view. I desire to emphasize the point that in these spinal fluid reports there are certain constituents of the spinal fluid that might be of some importance to the clinician; for instance, acetone in diabetes and urea in uremia, but from a clinical point of view, I should say there is little value in performing a lumbar puncture in diabetes.

Dr. Sachs: In connection with the urea content in nephritis, the statement is made that "A urea content of 0.1 per cent is without prognostic significance; a content of 0.1 per cent to 0.2 per cent in many instances is indicative of a fatal termination." Would you limit that strictly to 0.1 per cent; that is, does the fatality increase, say, with 0.1 per cent to 0.12 per cent?

Dr. Alpers: Those figures are taken from a paper by Soper and Granat, and from the statistics that they published, the cases which did give a figure of from 0.1 per cent to 0.2 per cent certainly did die very shortly. I cannot speak from personal experience.

Dr. Sachs: So that 0.1 per cent would seem to be the limit of safety in those cases?

Dr. Alpers: Yes.

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Chapter XXVIII

CARBON MONOXIDE ASPHYXIA, HEADACHE AND INTRACRANIAL PRESSURE

HENRY S. FORBES, M.D.

THE admirable work of Lewis Weed upon intracranial dynamics has stimulated further investigation in many laboratories. Some years ago, using Weed's methods, Stanley Cobb and I began to study the physiology of headache. We were particularly interested in the type of headache common among those exposed to automobile exhaust gas or to leaking illuminating gas fixtures, gas ranges and similar appliances. The headache is rather characteristic and is often described as "like a band of iron pressing tightly about the temples," or "as if one's forehead were in a vise." It is usually temporal, sometimes parietal. It may last for hours after exposure to the gas, if the exposure has been severe; is usually constant, and sometimes is accompanied by dizziness, nausea and anorexia, rarely by vomiting. Shaking the head suddenly is painful, also turning the eyes far to one side, and pressing on the eyeballs.

This headache is due to partial asphyxia or lack of oxygen in the inhaled carbon monoxide gas. It is true that illuminating gas contains other poisonous constituents (e.g., benzol) which may be important in long repeated daily exposures, but in acute gassing carbon monoxide alone is responsible for the symptoms.

Action of Carbon Monoxide Gas on the Living Body

Pure CO gas was used for our experimental work, and it may be of interest to consider the most recent views regarding the action of this gas upon the living body. The following statements are agreed to by the four men who may be considered the best authorities on the subject: Haldane in England, Lewin in Germany, Nicloux in France, and Yandell Henderson in the United States.

Carbon monoxide has no direct toxic action upon nervous tissue. This is now firmly established. Its injurious nature is due solely to its property of uniting with hemoglobin and thus excluding

oxygen from the tissues.[1,2,3,4] The union with hemoglobin is not a stable compound; consequently if the individual is withdrawn from the gas and respiration continues normally, oxygen will replace the CO, which is then eliminated by the lungs; the red cell is not injured, and normal oxygen transport is resumed. It takes time, usually some hours, completely to eliminate the gas if the blood has been highly saturated, and damage to the central nervous system may have already occurred. Lasting damage, however, happens, in so far as our experience goes, only with intense gassing, to the point of deep coma. Mild gassing, frequently repeated, causes no organic changes except those involved in acclimatization to low oxygen from any cause: polycythemia,[5] etc. Although a great variety of lesions, optic atrophy, multiple neuritis, etc., have been reported clinically following mild gassing, under controlled conditions, no such lesions, I believe, have been demonstrated. But even such mild gassing may be productive of distressing and temporarily crippling symptoms, comparable to "air staleness" in aviators.

The central nervous system is certainly the most sensitive of tissues in its reaction to oxygen want, a slight degree of asphyxia usually causing headache, dizziness, irritability and a sense of fatigue. Since Henderson and Haggard[6] by actual air analysis have shown that New York streets during heavy traffic hours may contain sufficient concentrations of carbon monoxide to cause such symptoms, and Hamilton,[7] in testing the blood of a group of garage workers for the gas, found 65 per cent positive, it seems important that practising physicians should be alert to establish the diagnosis.

Tannic Precipitation Test for Carbon Monoxide Hemoglobin

The tannic precipitation test for CO hemoglobin is simple and accurate A drop of the patient's blood is diluted in a ratio of one to five with distilled water and an equal volume of freshly-made 2 per cent solution of tannic acid added. This can be done with an ordinary white blood cell pipette. A red precipitate forms. If kept overnight, still in the pipette to exclude air from the surface, normal blood becomes gray-brown; CO blood retains a red tint. The test requires for control a drop of blood taken at the same time from someone who has not been exposed to the gas. The technique developed by the U. S. Bureau of Mines for quantitative determinations is described by Sayers et al.[8] It should be kept in mind that the patient should be examined while at work in the suspected atmosphere or within a few minutes, since the gas is soon eliminated by the lungs in fresh air.

Turning to the experimental work, the methods were as follows: Changes in cerebrospinal fluid pressure were recorded in anesthetized animals subjected to intense asphyxia, such as would cause severe headache in man. Cisternal puncture was performed and the needle connected with a 1 mm. bore glass manometer. The changes in the retinal vessels were followed by the ophthalmoscope, and alterations in brain bulk were observed through a trephine opening.

Findings

The findings were as follows: During asphyxia a marked rise in cerebrospinal fluid pressure occurred shortly after the animal began to breathe the gas. A series of sixteen animals all showed this rise, which followed almost immediately a rise in arterial pressure, and at the same time the ophthalmoscope showed a dilatation of the retinal veins. Later, after prolonged asphyxia, a gradual increase in brain volume was observed through a trephine opening. In one case symptoms of cerebral compression developed in spite of the trephine, and intravenous hypertonic salt was given. Complete relief from the compression symptoms followed within twenty minutes.

In 2 clinical cases of poïsoning by illuminating gas, one at the Boston City Hospital reported by Fremont-Smith,[9] the other at the Massachusetts General Hospital, high cerebrospinal fluid pressures (285 mm. in one case, and 250 mm. in the other) were found, associated with stupor and severe headache. Hypertonic salt solution (15 per cent sodium chloride) was given intravenously in both cases, and in each the symptoms were promptly relieved. In a third illuminating gas case at the Massachusetts General Hospital, stupor was present without a high cerebrospinal fluid pressure. There seemed no indication for hypertonic salt, and none was given. After several days the patient recovered, but with considerable mental impairment. The period of asphyxia had evidently been so intense as to cause permanent damage.

Henderson and Haggard have made a most practical suggestion to reduce effectively the objectionable concentrations of exhaust gas now breathed by many thousands of persons in all our large cities. Their recommendation is to install vertical exhausts on trucks and on all cars with permanent tops. The exhaust gas should be discharged upward out of the respiratory zone of street air,

instead of along the ground as at present, a method which contaminates this zone and invades adjacent shops, offices and residences. In garages vertical exhaust upward renders the problem of ventilation simple, since the heat of the gas holds it against the ceiling and thus it is easily removed through any ventilator in the roof. Under present conditions proper ventilation of garages is extremely difficult to carry out.

Treatment

Treatment of symptoms due to mild gassing consists merely in recognition of the cause and in prevention of further exposure.

Concerning treatment of severe acute cases, within the last two years the Committee on Resuscitation, appointed by request of the American Gas Association, has done important work. They emphasize the value of immediate manual artificial respiration by the Schäfer method in contrast to any mechanical device. They also recommend the administration of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen, introduced by Henderson and Haggard, to hasten carbon monoxide elimination. This has come into extensive use and has proved of real value. In comatose cases, if the cerebrospinal fluid pressure is elevated, hypertonic saline intravenously or magnesium sulphate by rectum may restore normal pressure and relieve the symptoms of compression. The reason for advocating hypertonic solutions rather than simple lumbar puncture and removal of fluid is that there is experimental and clinical evidence for the existence of cerebral edema in these cases. Simple removal of fluid would not influence this condition, but hypertonic solutions are known to be effective in relieving cerebral edema.

* * *

The following remarks were made by Dr. Frank Fremont-Smith in regard to one of the cases discussed by Dr. Forbes:

The only comment I would wish to make is that the recovery in one case, where the hypertonic salt was given, was rather striking. The spinal fluid pressure, taken within two hours after exposure to the gas, showed 285 millimeters of water pressure. The spinal fluid was drained slowly, 50 c.c. being removed and the pressure fell to 135 mm. The patient remained semi-comatose. Twenty-four hours later he could be roused only with difficulty, and when roused, complained bitterly of headache. The lumbar puncture was repeated,

a pressure reading taken, which was then 255 mm., a rise from 135 to almost its original level. No fluid was removed this time, only the few drops necessary to make the pressure readings being lost. One hundred c.c. of a 15 per cent sodium chloride solution were given intravenously. Within three hours the man was sitting up and eating a meal. This was a single case, and it may have been a coincidence, but it seemed very striking to us.

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Chapter XXIX

THE CEREBROSPINAL FLUID IN LEAD POISONING*

CARL V. WELLER, M.S., M.D., AND AILEEN DEAN CHRISTENSEN, A.B.

NOTWITHSTANDING restrictive and protective regulations and more or less effective educational endeavors, lead poisoning continues to hold its place in the first rank of industrial hazards, and to find its victims through the most unexpected sources among the non-industrial population as well. One can but question whether there has been any material decrease in the incidence of this condition. Much has been accomplished tending to protect the workers in such hitherto well-known hazardous trades as white lead manufacture, painting with hand brushes, pottery glazing, type founding and file cutting. At the same time, however, we are met by the phenomenal growth of new industries using lead, such, for example, as the storage battery industry, and the adoption of new mechanical processes, such as spray painting and machine typesetting, introducing new kinds of industrial hazard. Entirely new uses for certain organic compounds of lead have arisen which may give them nearly universal application, and these, too, must be taken into account. Moreover, conditions of previously unknown etiology are from time to time added to the list of lead diseases. A notable example appears to be the serous meningitis, so-called, of young children in the Far East. This, said by Suzuki and Kaneko[1] to be the fourth in rank among the important causes of infant mortality in Manchuria, was found by Hirai,[2] in 1923, to be due to the lead-containing powder used as a cosmetic by young mothers.

History

Although nervous system involvement in lead poisoning was known to the early medical writers, the growing appreciation of its importance is a matter of relatively recent date. Ramazzini,[3] in 1700, had written of potters that "first their hands begin to shake and tremble and then they become paralytic,

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splenetic and lethargic"; but it was Tanquerel des Planches[4] who, in 1838, by the collection, analysis and discussion of 72 cases of lead encephalopathy, firmly established the nosology of this condition. From that date the literature has multiplied with great rapidity until there are now some 300 titles dealing specifically with lead encephalopathy. Concealed under less definite titular designation among the 5000 or more references in a fairly complete bibliography of lead poisoning, there are numerous other clinical reports. The many reported cases, with their great variety of symptomatology, include those in which evidences of meningeal involvement appear, sometimes to the extent of dominating the clinical picture. Thus the terms saturnine meningitis and saturnine meningoencephalitis came to be applied to certain cases in which lead was thought to play at least a contributory part. Such were those reported by Lyman[5] and by Bensaude and Rivet,[6] the former in 1891 and the latter in 1904.

Mosny and Malloizel[7] were the first to establish a morphological basis upon which a clinical saturnine meningitis could be founded. Writing in 1904, they described the practically constant occurrence in cases of lead poisoning of a lymphocytosis of the cerebrospinal fluid. In various patients these authors found 5 to 15, 3 to 6, 4 to 11, 1 to 2 and 9 to 23 lymphocytes per field. During an encephalopathic crisis the last of these patients showed as many as 111 lymphocytes per field. They conclude, "It is possible, through examination of the cerebrospinal fluid, to measure, as it were, the impregnation of the nervous system by lead, to assign to their true cause similar nervous manifestations, and, finally, to give to the worker such advice as will enable him to safeguard his health." The occurrence of a type of lead encephalopathy characterized, among other things, by the presence of a lymphocytosis in the cerebrospinal fluid, was henceforth recognized by the French clinicians[8–20] who published during the next eight years numerous articles dealing with the signs and symptoms of saturnine meningoencephalopathy.

During this period of great interest in saturnine meningitis on the part of the French clinicians, Spiller,[21] in this country, had emphasized the meningeal endothelial proliferation in a painter who had shown evidence of central nervous system changes during life. No report of the state of the cerebrospinal fluid was made. Maas,[22] likewise, reported a group of cases which he believed to exhibit a special form of lead encephalopathy, a hydrocephalus acquisitus which, in his title, he put in the group of meningitis serosa. Again, no report upon the cerebrospinal fluid was made.

In the succeeding years there have been only occasional articles dealing with a meningeal reaction or with changes in the cerebrospinal fluid in cases of lead poisoning, but, with the increasing elaboration of method of microchemical investigation, more complete studies of the fluid have been made.

Plate,[23] in 1913, reported a case which he had diagnosed as meningitis saturnina, commented on the rarity of this condition as revealed by the German literature and acknowledged his indebtedness to the French for the possibility of making the diagnosis. His patient showed a cerebrospinal fluid pressure of 440 mm. of water and a cell count of 258 on one occasion and 270 per cubic millimeter on another, almost all lymphocytes, falling to 14 in about seven weeks. In the same year Boveri[24] discussed the meningeal reaction in chronic lead poisoning and concluded that the meningeal reaction due to

lead is manifested by an increase of pressure ranging from 30 to 50 cms. (Kroenig), by an increase in globulin content demonstrable by the Nonne and Noguchi tests and by a cellular reaction usually less pronounced than in tabes and general paresis.

In a fatal case of lead poisoning in a child of five years who had gnawed the paint from his crib, Thomas and Blackfan (1914)[25] found on various occasions a clear, sterile cerebrospinal fluid with cells chiefly mononuclear, ranging from 20 to 40 per cubic millimeter. The first puncture showed a greatly increased pressure, not subsequently noted. The Noguchi test was positive for globulin, Fehling's test positive for reducing substance and the Wassermann reaction was negative. A similar source supplied the lead ingested by the nineteen-months-old child described by Strong[26] in 1920. Three specimens of spinal fluid are reported in tabulated form. A slight increase in pressure was noted once. The cells were less than 10 on two occasions and less than 20 per cubic millimeter on the third. However, they were mostly polymorphonuclear leucocytes. Tests for albumin, globulin and reducing substance were positive in all three specimens.

In the second of the series of cases of lead meningoencephalopathy reported in 1921 by Barron and Habein,[27] the cerebrospinal fluid was examined and found to be clear, with the pressure slightly increased. There were 6 cells per cubic millimeter, and the Nonne, colloidal gold and Wassermann tests were all negative.

The following year Norton[28] found in a baby, poisoned by the lead acetate contained in an ointment applied to the mother's eczematous breast, a cerebrospinal fluid which was clear, faintly yellow, gave positive globulin and sugar tests and showed a cell count of 12 per cubic millimeter, of which 95 per cent were polymorphonuclear leucocytes. Three days later, when the child was still having convulsions, its fluid was clear, pressure much increased, cell count 30 per cubic millimeter, of which 3 were polymorphonuclear leucocytes and 27 lymphocytes, and the globulin was increased.

Kraffczyk (1923)[29] reported three cerebrospinal fluid specimens from a lead worker known to have had chronic lead poisoning for fourteen or fifteen years. This man gave evidence of a cerebellar ataxia and had frequent epileptiform convulsions. On the first occasion the fluid was clear, pressure 165 mm., albumin increased and there was a slight lymphocytosis. A little later the pressure was found to be 250 mm. and the Nonne, Phase 1, was negative. Three years after the first puncture the pressure was 100 mm., there was but a trace of albumin and no cellular elements were found.

Within the present year the interesting paper of Suzuki and Kaneko,[1] to which reference has already been made, records the findings in the cerebrospinal fluid of two cases of so-called serous meningitis of infants, due in each instance to a white face powder, lead-containing, used by the mother. In the first infant there was found a first pressure of 400 mm. of water which dropped to 200 mm. after the removal of 30 c.c. The fluid was clear. Pandy, Noguchi and Nonne-Apelt, Phase 1, were all positive, as was also the Haines test for sugar. The cell count was 4 per cubic millimeter, equally divided between polymorphonuclear leucocytes and small lymphocytes. The albumin content was found to be 0.066 per cent and the calcium content 4.884 per cent. In the second case the pressure was 400 mm., falling to 150 mm., the globulin

tests were positive, albumin increased and the sugar reaction was positive. The first cell count on this patient gave 6 lymphocytes and 14 polymorphonuclear leucocytes per cubic millimeter. A later count showed 18 small lymphocytes, 30 polymorphonuclear leucocytes and 4 red blood cells per cubic millimeter. One of these authors had previously reported on the increase of sugar in the cerebrospinal fluid in this type of meningitis.

This brief résumé of the reported findings in the cerebrospinal fluid, while not complete, will suffice to show the trend of the observations that have been made.

Three points emphasized by the French writers and accepted by Boveri,[24] Plate[23] and others still hold good. These are increased pressure, increased cells, chiefly lymphocytes, and increased albumin (globulin) content. Each of these points requires a brief discussion.

There is general agreement that the pressure of the cerebrospinal fluid is increased in lead meningoencephalopathy. In several cases in which more than one puncture was made, there is evidence that a higher pressure was found early in the disease and that following withdrawal and elimination of lead the pressure fell coincident with the clinical improvement. Lacking information as to the technique employed in taking the pressure, the author's statement that the pressure was increased is of more significance than the numerical expression.

An increased cell count is found in practically all of the reported cases, but it becomes very evident that the cytological picture is not that of a simple lymphocytosis alone, for very frequently a polymorphonuclear reaction of slight or moderate degree has been encountered. All the spinal fluid specimens were sterile. The higher percentages of polymorphonuclears have been found more particularly in children, while most of the adult cases have shown a lymphocytosis of 60, 90 or even 97 per cent. It may be that those cases which are relatively acute, or in which a massive poisoning occurs, are more apt to show a greater number of polymorphonuclear cells. This point requires further illumination from clinical data.

The albumin increase of the earlier writers is substantiated by the positive globulin tests shown by practically all of the more recent cases. Boveri[24] states that in some fluids there is an increase in albumin and a decrease in cells. Such a dissociation of these two factors is not borne out by other observations.

Suzuki and Kaneko[1] have reported an increased sugar content in the cerebrospinal fluid of children showing this condition. All of the

examples in which tests for sugar are given seem to be in accord with this view. In several cases no information is given as to whether a pathological increase is meant when a positive test is recorded, for a normal fluid gives a slight reduction. If further observations show an increased sugar content to be a constant finding in lead meningoencephalitis, a new point of diagnostic importance will have been added.

While the Wassermann reaction has been negative in the reported cases, the older literature has frequently emphasized the apparently augmented meningeal reaction in cases in which syphilis and lead poisoning were simultaneous causal factors. It is beyond the scope of this paper to go into this interesting question. If true, as seems probable, we must expect a positive Wassermann test in a larger percentage of cases of lead meningoencephalopathy than the laws of chance alone would demand. Lereboullet and Faure-Beaulieu[30] believed the Wassermann reaction to be more readily positive in syphilis plus lead poisoning than in syphilis alone.

The clinical evidence at hand, therefore, gives, as the important findings in the human cerebrospinal fluid in cases of lead poisoning with meningoencephalopathy, a moderately increased pressure; a clear, colorless or slightly yellow, sterile fluid; an increased cell count often chiefly lymphocytic, sometimes polymorphonuclear; positive globulin tests; sugar present and probably increased.

Agreement between the Laboratory Findings in Clinical, and the Histopathology of Experimental, Lead Meningo-encephalopathy

If this question be approached from the experimental side a number of interesting problems at once present themselves. One of these is whether or not there can be induced in experimental animals any histological changes which would be compatible with the production of a cerebrospinal fluid of the type found clinically.

It is well known that in most laboratory animals signs of marked central nervous system involvement can be produced by the administration of lead. Epileptiform convulsions constitute the most striking manifestation. Such have been noted by Rosenstein,[31] McCarthy,[32] Catalano,[33] Suzuki and Kaneko[1] and others as occurring in dogs. In rabbits, convulsions rarely occur until the animal is about to die, when a single convulsion may close the picture. In guinea pigs, as was noted by Popow[34] in 1885, epileptiform

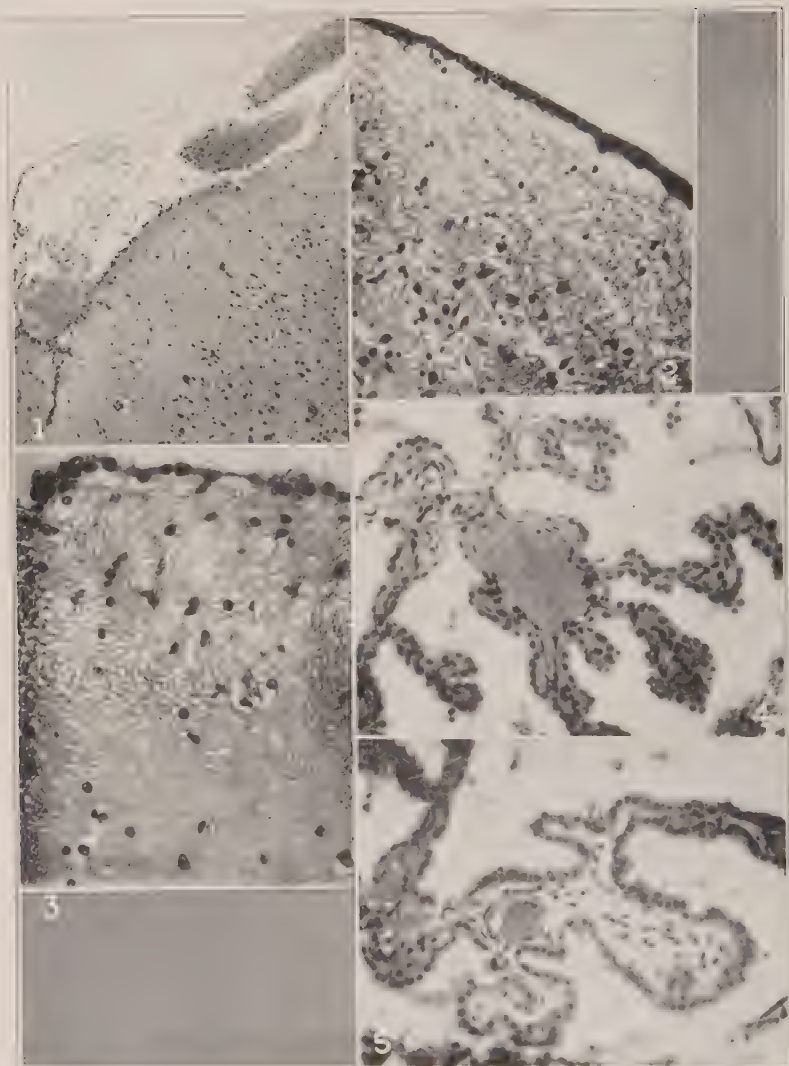

FIG. 69-A.

A. (1) Marked meningeal congestion and edema, with moderate lymphocytic infiltration. (Hemalum and eosin stain. Zeiss obj. B, no ocular.) This, and the four following photomicrographs, were made from guinea pigs dying in convulsions after four doses of commercial white lead, given by mouth.

(2) Extreme edema beneath the ventricular ependyma, with some swelling of the ependymal cells. (Hemalum and eosin stain. Zeiss obj. B, compensating ocular No. 4.) (*Caption for Fig. 69-A continued on following page.*)

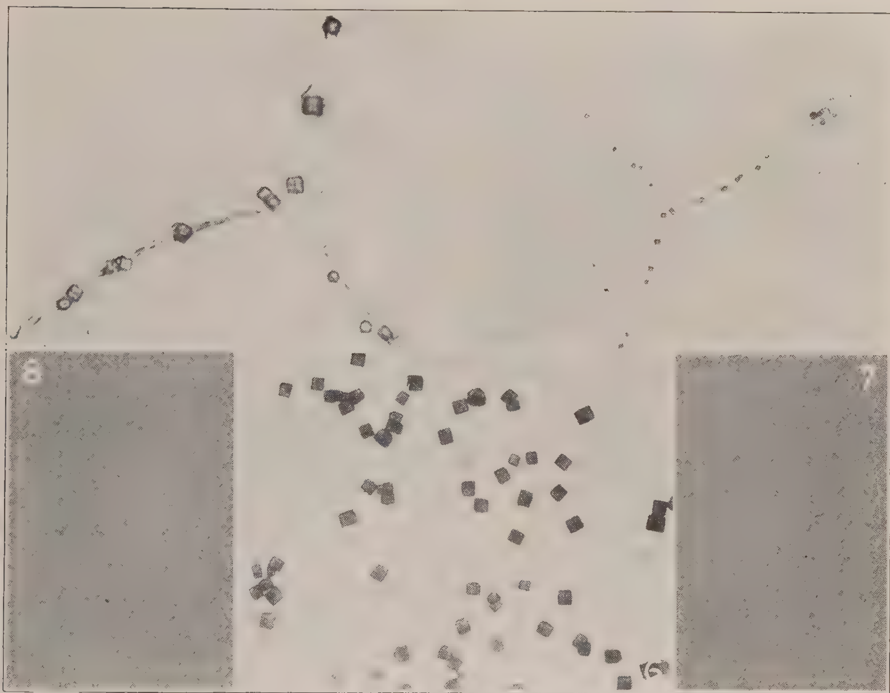

FIG. 69-B.

(3) Extreme edema of the brain substance near a lateral ventricle, with swelling and hydropic change of the ventricular ependyma. (Hemalum and eosin stain. Zeiss obj. B, compensating ocular No. 4.)

(4) Chorioid plexus with marked congestion and swelling of the ependymal cells, giving them a markedly hypertrophic appearance. (Hemalum and eosin stain. Zeiss obj. B, compensating ocular No. 4.)

(5) Congestion of the chorioid plexus with marked edema in the villi shown in this field. Swelling of the ependymal cells. (Hemalum and eosin stain. Zeiss obj. B, compensating ocular No. 4.)

B. (6) Photomicrograph of the hexanitrite crystals of cesium, copper and lead as prepared from a dilute solution of a pure lead salt. Note the uniformity of outline. (Balsam mount after drying. Zeiss obj. B, compensating ocular No. 4.)

(7) Characteristic lead crystals (hexanitrite) as prepared from 5 c.c. of human cerebrospinal fluid to which one microgram (.000001 gm.) of lead acetate had been added. Note the grouping of the crystals along the residual material. (Zeiss obj. B, compensating ocular No. 4.)

(8) A high-power view of isolated crystals from the same preparation. The photomicrographic plate reveals the refractive properties of these crystals. In shape they are still characteristic in spite of their small size. (Zeiss obj. DD, compensating ocular No. 4.)

convulsions, with both clonic and tonic phases, can be produced with great constancy by the oral administration of lead compounds. The clinical picture of the convulsive type of human lead meningo-encephalopathy can be duplicated in these animals in a most striking fashion. Also, after a bout of convulsions a state of active dementia may persist. Such an animal has been noted as continuing to circle about its cage in an unseeing, aimless manner for hours at a time. Convulsions may be produced in guinea pigs by a few relatively large doses of lead by mouth or they may develop after a long period of time, during which the administration of lead has been so carefully controlled that no marked loss of weight occurs.

Within the limits of this paper no complete report upon the general histopathology of the central nervous system of the animals in which we have produced an experimental lead meningo-encephalopathy can be made. We wish to call attention, however, to the fact that even in the most acutely produced convulsive type of the disease, there are changes present which are in full accord with the human cerebrospinal fluid findings. As is shown in Figure 69, there is a venous congestion which is more marked in the pia and in the chorioid plexus than in the brain substance; there are also an extreme edema, most noticeable beneath the ventricular ependyma and in the inner meninges, and a slight and rather diffuse lymphocytic infiltration in the inner meninges, especially about the pons and cerebellum. The ependymal cells of the chorioid plexus have a swollen appearance, which is shown by the parietal ependymal cells as well. The extreme edema of the brain substance presents areas of marked separation of the glial fibers, approaching a liquefaction necrosis. The guinea pigs from which the photomicrographs illustrating these changes were made had each received by mouth on successive days four doses of commercial white lead, 0.126 gm. to the average dose, administered in No. 5 gelatin capsules after being ground to a soft paste with starch and linseed oil, a method of administration which we have used in a variety of lead experiments during the past twelve years. These animals commenced having convulsions on the fifth day and died on the fifth to eighth day after the first dose. The congestion, edema and swelling of the ependymal cells are in accord with the increased pressure found clinically and probably explain the increased globulin as well. The lymphocytic infiltrations fit in with the free lymphocytes of the fluid. We find no evidence of a polynuclear reaction. We wish to call attention to the absence of

perivascular mantling such as is found in the so-called spontaneous encephalitis of rabbits and to record that we have selected the guinea pig to furnish the illustrative material at this point in our argument because of the unfortunate confusion between spontaneous and experimentally produced rabbit encephalitis which has crept into the literature.

The Lead Content of the Cerebrospinal Fluid

Those features of the cerebrospinal fluid which we have found to be common to practically all of the cases of lead meningoencephalopathy in which the fluid has been described are not such as to make a diagnosis of lead poisoning certain in and of themselves. While they should be of great value in eliminating certain other conditions and might confirm a suspected case, on such findings alone the possibility of an early tuberculous meningitis or of a luetic meningitis could not be excluded. Negative evidence such as might be obtained from the Wassermann test or from animal inoculation might assist, and knowledge of exposure to a lead hazard, with the presence of a lead line or of chromatophilia and basophilic stippling of the red cells, would practically clinch the diagnosis. Lacking these, however, it would be valuable if the diagnosis could be confirmed by the identification of lead in the cerebrospinal fluid itself. Notwithstanding the general belief that most metallic substances do not pass through the chorioid plexus or the meninges, it seems highly probable that with lead present in the blood stream some amount of the metal, perhaps exceedingly minute, must enter the fluid.

Camus,[35, 36] in experiments which have been largely ignored by recent writers, obtained evidence suggesting that the convulsions of lead meningoencephalopathy might be due in some way to the presence of lead in the cerebrospinal fluid. He found that by injecting small amounts, 1 or 2 c.c., of a 1 to 500 solution, of lead chloride into the cerebrospinal fluid of a dog he could produce, after a latent period of two or three days, restlessness, crises of agitation, the aspect of hallucinations and epileptiform convulsions, followed by semi-coma and death in twenty-four to forty-eight hours. These results were entirely like those produced when lead is given orally, or by either intravenous or subcutaneous injection. Similar results did not follow if the lead solution was injected into the parenchyma of the brain. Lead butyrate was used successfully

in the spinal canal showing that the effect was not due to the chlorine.

Strong,[26] in 1920, failed to find lead in the cerebrospinal fluid of his case of lead meningitis. At that time he discussed the possibility of lead reaching the cerebrospinal fluid through increased permeability of the chorioid plexus or other pathological change. He wrote, "but conclusions can only be reached by experimental work with lead." He apparently was not aware that there were already in the literature two reports claiming the successful demonstration of lead in the cerebrospinal fluid of patients showing a lead meningoencephalopathy. No report has been found of any experimental investigation of this point. Marie,[37] in 1908, gave the clinical history of a patient in whose cerebrospinal fluid Trillat found the characteristic reaction of lead, but in an amount too small to permit quantitative estimation. The subject was a painter, forty-five years old, who was also a general paretic, having had syphilis twenty years before. Lead was subsequently demonstrated in the brain to the computed amount of 4.435 gms., but with such a difference between the amounts in the two hemispheres as to raise some question. The method used upon the cerebrospinal fluid was that known to the French as the procedure of Trillat. This consists (Heim, Agasse-Lafont and Feil[38]) in destruction of the organic matter followed by colorimetric estimation, using basic tetramethyl diphenylmethane in acetic acid solution. This method is said to be sensitive to 0.00002 or 0.00001 mgm.

The only other positive result for lead in the cerebrospinal fluid was also obtained by the method of Trillat. This was reported by Gouget[39] in 1911, the estimation having been made by Hébert. Lead to the amount of 0.05 mgm. was found in 14 c.c. of cerebrospinal fluid. The patient was a color maker working with lead pigments. He had had lead colic previously. One week after admission he had an epileptiform crisis followed by seven or eight other seizures on the same day and more severe attacks on the next day. Lead to the amount of 0.03 mgm. was recovered from 155 gms. of brain substance, equivalent to 0.23 mgm. for the entire brain. All other known attempts have given negative results.

Unless some mechanism exists by which a proportionately greater amount of lead reaches the cerebrospinal fluid, or by which it is retained and concentrated in the fluid, as compared to the parenchyma of the brain and spinal cord, one can expect but minute amounts of lead to be present therein. Considering the

facts that the cerebrospinal fluid is a changing, circulating medium, perhaps renewed several times in twenty-four hours, and that sometimes but a fraction of a milligram of lead can be found in the entire brain of a fatal case of lead poisoning, not much can be expected from a clinical specimen consisting of from 5 to 20 c.c. We know very little, however, not only about the rate of absorption of the cerebrospinal fluid but also about the possibility of selective mechanisms being concerned. There is abundant evidence that lead becomes at least temporarily fixed in certain tissues and thereby withdrawn, in part, from the general circulation.

The work of the Harvard group on lead and of L. T. Fairhall,[40,41] in particular, has made it possible to do satisfactory qualitative tests for exceedingly small amounts of lead present in relatively large quantities of biological material. Results of chemical research upon the body fluids and organs in cases of lead poisoning have formerly been notoriously inconsistent and uncertain. There can be but little doubt that much of the older work is without value. Lead has escaped detection and other substances have been included as lead, so that both minus and plus errors have occurred. From both quantitative and qualitative standpoints the newer methods are altogether superior. The successful prosecution of our present research has depended largely upon the work of Fairhall[41] in refining the technique of the hexanitrite test for lead. Mott,[42] in 1909, had used this method on the brain of a case of chronic lead encephalitis without success.

In endeavoring to demonstrate the passage of lead into the cerebrospinal fluid by experimental means, it was found necessary to use rabbits. The guinea pig does not supply a sufficient amount of fluid, and it was inexpedient to use dogs at the time the work was being carried out. In many respects the dog would be the animal of choice but the rabbit has one advantage in that it withstands heavy dosage with lead with but little probability of sudden death in convulsions. Lead was administered in some cases by subcutaneous injection of 1 per cent lead acetate in varying amounts. To most of the animals lead was given by mouth in capsules containing a known amount of commercial white lead. Lead administration was continued for from two days to two months before the animals were used. The fluid was obtained by killing the animal with massive chloroform asphyxia, cutting down upon the cervical vertebrae and withdrawing the cerebrospinal fluid with a fine hypodermic needle inserted somewhat to one side of the midline

between the occiput and the first cervical vertebra, the point of the needle being directed somewhat mesially and kept close to the meninges. From 0.8 to 1.2 c.c. of clear fluid were usually obtained. Occasional contamination with blood was encountered.

In our first attempts to demonstrate lead, in which fifteen rabbits were used, we employed Fairhall's[40] volumetric method in which, after proper preparation of the unknown, the lead is precipitated as the sulphide, dissolved in nitric acid, reprecipitated as the chromate, filtered, dissolved in hydrochloric acid, excess of potassium iodide added and the liberated iodine titrated with sodium thiosulphate. In our work it was impossible to differentiate, by this method, between the cerebrospinal fluid of our lead-treated rabbits and that of normal rabbits. We were forced to conclude that either lead did not reach the cerebrospinal fluid at all or was not present in sufficient amount to respond to the test. Fairhall[40] advised against the use of this method for amounts of 0.05 mgm. of lead, or less. After thorough trial this method was therefore abandoned.

Recourse was then had to the most successful microchemical test for lead, the hexanitrite test. Although looked upon as uncertain by most chemists who had worked with it, Fairhall[41] had apparently produced a very promising standardized technique. In the second period of our research, use was made of Fairhall's method, except that the more sensitive cesium salt was used to replace the potassium in the hexanitrite crystals without precipitation as the sulphide, with added copper to entrain the lead. It was hoped that the precipitation step would not be necessary in view of the small amount of inorganic material present in cerebrospinal fluid.

Using the known solution directly upon a slide, we found that a very satisfactory test for lead could be obtained from 0.5 micrograms (0.0000005 gm.) of lead acetate and a positive test, the crystals being found with some difficulty, with as little as 0.2 micrograms.

Four lead-treated rabbits gave positive lead tests in the cerebrospinal fluid, but we then found a few hexanitrite crystals from the fluid of a normal rabbit, indicating contamination. This source of extraneous lead was finally determined to be in the potassium nitrite. After repurification of this and substitution of nitric acid which had been redistilled, no further difficulty was experienced from positive tests in control material. The four positive findings could not be accepted as proof of the passage of lead,

although they revealed a larger amount of lead than was shown by the false positive on a normal rabbit.

Eight additional animals were utilized after substituting the recrystallized potassium nitrite. Of these, one only gave a strong positive test. The negative findings in the other animals served as an effective control of the reagents and glassware used. A careful review of the experiment revealed no known opportunity for contamination in the positive case and this result was allowed to stand as a true positive.

Through the cooperation of Dr. C. D. Camp of the University Hospital and of Dr. A. M. Barrett of the State Psychopathic Hospital, we were provided with human cerebrospinal fluid. That from two patients, whose history led us to believe that lead poisoning might be present, failed to show lead by the method we were then using. Likewise, when minute quantities of lead were added to normal fluids and these were incubated for several hours in the hope of simulating the organic binding of the lead as it occurs in the body, we found that the lead could not be demonstrated consistently. The inorganic material interfered so seriously with the test as to invalidate it. When, however, we used the method suggested by Fairhall,[41] of concentrating the lead by precipitating it as a sulphide together with a certain amount of copper, centrifugating and washing the precipitate, and then redissolving and carrying out the hexanitrite test, we found no difficulty at all in demonstrating 0.000001 gm. of lead acetate added to 5 c.c. of human cerebrospinal fluid. So abundant were the crystals formed from but one-half of the residue in this instance that there is no doubt that with this modification the test would prove positive for quantities considerably smaller than the one stated, approximating the lower limit for a positive test with lead acetate added to water alone.

Since adopting our final procedure, which seems to have overcome all of the difficulties from the chemical side, positive results have been obtained for lead from the cerebrospinal fluids of three additional rabbits to which four and five capsules of commercial white lead, averaging 0.86 gm., had been administered by mouth. In two of these fluids there was a trace of blood, shown by a faint pinkish tint when viewed by white light. We do not know whether this represented a technical contamination or a slight hemorrhagic exudation. Such red blood cells as were present were removed by centrifugation before chemical analysis. If any blood plasma

were present, it would lessen the value of these two examples as used to prove the transmission of lead into the cerebrospinal fluid. In the third instance there were no circumstances which would lead us to question its validity.

We believe that we have demonstrated the transmission of lead, administered by mouth, to the cerebrospinal fluid. However, we wish to make only a preliminary report upon this point at this time, reserving final judgment until further series of animals can be tried out. We believe that the procedure outlined below provides the chemical means for carrying out this research and for examining for lead the cerebrospinal fluid of patients thought to have lead meningoencephalopathy. We anticipate that certain of the organic compounds of lead may be found to enter the cerebrospinal fluid with greater ease than when lead is inspired or ingested in inorganic form. There seems to be a marked difference in individual animals as to the extent to which lead enters. This may be due to varying conditions affecting absorption from the gastrointestinal tract.

Adaptation of the Hexanitrite Test, as Standardized by Fairhall,[41] to the Examination of Human Cerebrospinal Fluid

PROCEDURE

1. Evaporate the available cerebrospinal fluid to dryness in a small Kjeldahl flask.
2. Decompose the organic matter by the addition of 5 c.c. of nitric acid, added 1 c.c. at a time. More acid may be needed to effect decolorization. Finally, add ½ to 1 c.c. of sulphuric acid and continue heating until no more fumes are evolved.
3. Dissolve residue completely in hydrochloric acid, using 1 to 2 c.c., and wash into a test tube holding at least 20 c.c.
4. Neutralize with strong sodium hydroxide solution, and make slightly acid to methyl orange with hydrochloric acid.
5. Add 1 c.c. of saturated ammonium sulphate and 1 to 2 drops of 2 per cent copper acetate.
6. Precipitate by saturation with hydrogen sulphide and concentrate the precipitate in one centrifuge tube by centrifugating and decanting the supernatant liquid.
7. Wash precipitate in the same tube at least three times, draining the water from the precipitate after each centrifugation.
8. After the final washing, add 2 to 3 drops of nitric acid to the precipitate in the centrifuge tube and stand the tube in a beaker of boiling water until the precipitate is dissolved.

9. Draw up the resulting solution in a capillary tube and evaporate to dryness on a microscopical slide, keeping the area small by applying but one drop at a time.

10. Add 5 to 10 cu. mm. of 4 per cent sodium acetate solution, mixing with a glass needle to dissolve all the residue, but taking care not to enlarge greatly the area of the fluid upon the slide.

11. Evaporate to dryness on the slide and chill on ice.

12. Add 5 cu. mm. of 10 per cent acetic acid and place centrally a small crystal of potassium nitrite and a small crystal of cesium chloride.

13. Cover with a cover glass and examine with the high dry lens (4 mm.).

The presence of lead is shown by the highly characteristic crystals of the hexanitrite, $CsCuPb(NO_2)_6$. These crystals are small yellowish-red to brownish-black square plates and cubes. The color is dependent upon the thickness of the particular crystal. A few oblong forms will be found in examining a large number of crystals as well as a few which appear unequally hexagonal. These latter are cubical or nearly cubical crystals, so poised as to present an angle toward the observer. In size, the crystals vary from those just capable of being resolved as squares with the high power of the microscope up to about 20 microns in diameter. They are highly characteristic and in examining many slides we have found no other crystalline structures with which they might be confused. Although averaging smaller than those made with the potassium salt, the cesium crystals show much less variation in form and their smallness becomes an advantage in making them appear brighter red and less dark in the field. To one experienced in the use of the compound microscope, their small size is no disadvantage. Since the addition of cesium renders the method about five times as sensitive as when potassium is used, we recommend it for the examination of the spinal fluid for lead.

The small amounts of sodium acetate solution and of dilute acetic acid required can be conveniently measured in routine work by calibrating home-made capillary pipettes. Such pipettes can be made to deliver a droplet of about 5 cu. mm. in volume.

One making use of this test should satisfy himself that the entire method can be run through in blank without evidence of contaminating lead. Difficulty, if met, will probably be due to the potassium nitrite, the nitric acid or the utensils used. Fairhall[41] gives a satisfactory method for the purification of potassium nitrite. We quote from him:

"Silver nitrate should be added to the filtered solution of potassium nitrite and the resulting precipitate of silver nitrite washed well with cold water. This silver nitrite is then dissolved in boiling water and an equivalent amount of pure potassium chloride added. The pure potassium nitrite in solution may then be crystallized by evaporating this solution to a small bulk."

The nitric acid may be freed from lead by redistilling, preferably from a silica flask. We have had no evidence of lead derived from our laboratory glassware. It is all allowed to lie for at least twenty-four hours in nitric acid and washed in distilled water before being used. We have used Pyrex glass Kjeldahl flasks of 50 c.c. capacity.

While this method may at first sight seem rather formidable, once one is assured of proper reagents, it offers no serious difficulties. It can be performed by anyone accustomed to such laboratory procedures as the Wassermann test

and routine blood counting. The entire method can be carried out in one and one-half hours, and during part of this period the full time of the technician is not required.

Summary

We have endeavored by combining in this paper material derived from historical, clinical and experimental fields to develop a definite conception of the cerebrospinal fluid in lead meningoencephalopathy. We have shown by selected references from the literature the gradual separation from the group of lead encephalopathy of a sub-group in which evidence of meningeal involvement plays an important part. The cerebrospinal fluid findings of this group have been summarized and found to be fairly constant, without in themselves being diagnostic. The value of the recognition of lead in the fluid itself, if it occurs there, at once becomes evident. Its successful recognition has twice been reported. Since administration of lead to laboratory animals by various methods, including injection into the spinal canal, produces a clinical condition entirely comparable to human lead meningoencephalopathy, with histological changes in accordance with the findings in the cerebrospinal fluid of human cases, experimental investigation of the fluid of animals is justified. Having, we believe, successfully demonstrated the passage of lead into the cerebrospinal fluid of lead-poisoned rabbits by means of Fairhall's[41] modification of the hexanitrite test, we have arranged an adaptation of this test suitable for the clinical laboratory examination of cerebrospinal fluid. If it is found that lead is transmitted to the fluid in human cases as it seems to be in the rabbit, this method should prove of great diagnostic value.

Conclusions

1. The cerebrospinal fluid in lead meningoencephalopathy is a clear sterile fluid showing increased pressure; increased cells, commonly mononuclear, sometimes polymorphonuclear in character; increased globulin content and probably increased sugar. Twice the recognition of lead in the cerebrospinal fluid has been reported in the literature.

2. In guinea pigs dying with clonic and tonic convulsions after ingestion of lead, the histological changes in the chorioid plexus, ependyma, brain substance and meninges are such as to be in accord with the cerebrospinal fluid changes found in human cases.

3. We believe that by the improved hexanitrite test (Fairhall) we have successfully demonstrated the passage of lead into the cerebrospinal fluid of lead-poisoned rabbits. This point requires further verification and will be the subject of a later report. There appears to be much variation in this respect among different animals receiving the same dosage.

4. We suggest that this test be used to ascertain whether a similar transmission of lead occurs in human lead meningo-encephalopathy, and we recommend its adoption as a diagnostic procedure if such should be found to be the case.

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Section VII

THE TREATMENT OF PATHOLOGICAL CONDITIONS THROUGH THE CEREBROSPINAL FLUID

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Chapter XXX

THE INTRAVERTEBRAL TREATMENT OF DISEASES OF THE CENTRAL NERVOUS SYSTEM, EXCLUSIVE OF THE INTRASPINAL TREATMENT OF CEREBROSPINAL SYPHILIS

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SINCE the first intraspinal injection by a direct puncture, reported by Corning[1] in 1885, many diseases have been treated by injections of equally numerous medicaments.

Intravertebral treatment of but two diseases has proved to be of positive value; namely, meningococcic meningitis and tetanus.

Occupying, as it does, a part in a general discussion upon cerebrospinal fluid, this communication does not contain the details of the treatment of any disease. A brief outline will be given of diseases treated by the subdural administration of specific or immune sera and of drugs; and also by drainage, irrigation and by miscellaneous procedures.

Meningococcic Meningitis

In May 1905, Jochmann[2] investigated a specific immune serum against meningococcic meningitis. In April, 1906, he reported, before the Kongress für Innere Medizin, the results of treatment of 38 cases of epidemic meningitis. At first he employed subcutaneous and later intraspinal injections.

About the same time Kolle and Wassermann[3] reported that they had also prepared an immune serum.

Flexner's[4] studies on an immune serum began after Jochmann's in 1905. In 1906 he reported a specific immune antimeningococcic serum which protected against experimental meningitis.

In 1908 Flexner and Jobling[5] published a comprehensive report of serum-treated cases.

Since then the specificity of this treatment has been accepted and the mortality of meningococcic meningitis has been reduced from a figure varying from 42.5 to 90 per cent to one of about 25 per cent.

The specificity of a serum depends upon the particular strain of the organism used in preparing it. Therefore, when Dopter[6] isolated an organism from the spinal fluid of a patient suffering with meningitis that had all of the morphological and cultural characteristics of the Micrococcus intercellularis meningitidis of Weichselbaum, but was not agglutinated by the usual meningococcus serum, it became necessary to produce sera of different valencies. Dopter called this organism the parameningococcus.

Wollstein[7] corroborated Dopter's observations and found a number of intermediate strains.

Gordon[8] discovered that the meningococci fell into four groups, which he designated as I, II, III and IV. Groups I and III and II and IV were closely related. Since then, a number of classifications have been made. At the Rockefeller Institute[9] two main groups, the normal and paranormal, and two or more intermediates are recognized.

Since the recognition of the different strains of the meningococcus, all are agreed that a polyvalent serum should be employed, pending the bacteriological report. When the strain has been ascertained, opinions differ as to whether a polyvalent or monovalent serum should be used. It may be assumed that until it is proved that a monovalent serum has a greater activity for a specific strain than a polyvalent serum against the same strain, a polyvalent serum has many advantages.

All meningococcic sera sold in interstate traffic in the United States are now required to be polyvalent, with a high titer against strains representing four different serological groups.

The successful treatment of meningococcic meningitis depends upon the early recognition of the disease and its early treatment with a serum of high potency and specificity for the type of infecting organism.

During the early months of the war the results of serum treatment were very unsatisfactory, because the strains of meningococci causing the infection were, in the majority of cases, different from those used in preparing the antimeningococcic serum which was employed.

Efficient treatment is dependent likewise upon the proper dosage, frequency of injection, continuation of treatment and upon the adequate distribution of the serum.

Because the title of this paper prohibits a description of the measures used in the treatment of meningococcic meningitis, it must not be understood that the intraspinal administration of serum constitutes all of the treatment. For example, intravenous injection of serum is strongly recommended by Herrick[10] and many others.

Whatever else may be done, the serum should always be introduced subdurally. Since it has been pointed out by Sophian[11] that symptoms of collapse are due to sudden increase of intracranial tension, the amount of serum injected should be slightly less than the amount of fluid withdrawn. The gravity method of injection described by Heiman[12] is the one of choice.

The following doses are considered safe for their respective ages: one to five years, 5 to 15 c.c.; five to ten years, 10 to 20 c.c.; ten to twenty years, 20 to 30 c.c., and over twenty years, 30 c.c. or more.

When, because of a viscid fluid, very little may be removed by spinal puncture, small doses frequently repeated are necessary.

The interval between injections should not exceed twenty-four hours. In severe cases the injection may be repeated every eight to twelve hours for three to four doses. One objection to very frequent injections is the production of a localized meningitis, with resulting long-lasting pain and paralysis of adjacent nerve roots.

With the administration of the serum, the meningococci become reduced in number and altered in size and staining property. The extracellular organisms become engulfed and finally disappear. Their viability is reduced and they can no longer be grown upon culture media.

The treatment should be continued until the clinical signs disappear, with a change to normal clearness of the fluid, and freedom from organisms. Usually the two go hand in hand. At times a turbid fluid may be present when all clinical signs have disappeared, and this may be the result of the injection of a foreign protein.

Other routes than the endolumbar are at times necessary for the introduction of the serum.

The injection of serum directly into the ventricles was first employed by Cushing and Sladen.[13]

Lewkowicz[14] especially advises intraventricular injection from the beginning of treatment, but except in complicated or severe cases it is not in general use.

When, because of a heavy exudate or meningeal adhesions, a block in the cerebrospinal system occurs, the intraventricular as well as other routes of injection must be employed. Because of the lack of danger and ease of cisterna magna puncture, as described by Wegeforth, Ayer and Essick[15] and amplified by Ayer,[16] injections in the dorsal and cervical regions are unnecessary.

Prior to the use of a specific serum, the mortality of meningococcic meningitis is given as from 20 to 75 per cent by Hirsch,[17] who collected the statistics of forty-one epidemics.

The figures compiled by Flexner show that the death rate in eighteen epidemics was between 42.5 and 90 per cent, varying in different epidemics and at different periods of the same epidemic. In treated cases Jochmann in 1906 had a death rate of 27 per cent, Lèvy of 16.2 per cent and 21.7 per cent in two epidemics, and Flexner and Jobling reported a mortality of 25 per cent in 393 cases.

Tetanus

Blumenthal and Jacob,[18] in 1898, first advocated the injection of antitoxin by means of lumbar puncture. In the past twenty-five years many hundreds of cases have received at least some of their treatment by this route and there has been a slow but steady growth of favorable opinion in regard to it.

Roux and Borrel[19] in the same year suggested direct injection of antitoxin into the substance of brain or cord.

Ransom,[20] in 1901, stated that subdural injections acted practically the same as injections anywhere in the subarachnoid space. In either case the antitoxin passed rapidly into the blood by way of lymph channels and only a trace was left in twenty-four hours.

Park,[21] after experimental work on guinea pigs, stated that "the results with intraspinal injections were considerably better than with intravenous and those with intravenous injections did much better than those receiving subcutaneous injections. The units required by the intraspinal method were less than by the other methods. Repeated large injections did not give any better results than a single sufficiently large injection."

Andrewes and Horder[22] found "that antitoxin is readily and quickly absorbed from the thecal space into the the circulation, so

that the intrathecal route practically accomplishes in a short time all that can be attained by intravenous injection with less risk of shock and with the possible, but unproved, advantage of some direct action upon the central nervous system.

Sherrington,[23] working on monkeys for the British Tetanus Committee in 1917, reported that all the controls, all those subcutaneously injected and all intramuscularly injected, had died, while 62.5 per cent was the mortality for those treated intravenously and 27.7 per cent for those treated intrathecally with tetanus antitoxin.

Golla,[24] from experimental work on animals, found the intrathecal route indubitably superior, but later,[25] in a review of war hospital statistics, felt that serum treatment in man had been a failure. He said, "By the time symptoms of tetanus appear, a sufficiency of toxin is already in the nervous system in such cases as would end fatally whether treated or not, whereas, in the milder cases, sufficient toxin to cause fatal tetanus is not manufactured." He concluded that, if allowance is made for the modification of the disease due to prophylaxis, there had been no diminution in the mortality.

It is extremely difficult to review profitably the results of the intrathecal treatment. Few cases have been treated by this route alone. Reported statistics usually do not differentiate the route of antitoxin administration. The well-known difference in virulence of the infection affords another difficulty.

Irons[26] urged the intraspinal injection of antitoxin in all cases of tetanus and found the mortality of 225 cases treated with serum was 61.77 per cent, while that of 21 cases treated without serum was 85.7 per cent. The number of cases receiving intraspinal treatment is not tabulated. His figures showed that those receiving injections on the second and third days did better than those receiving them on the first. This is due to the fact that the most acute and, of course, most unfavorable cases came to earlier attention.

Park[27] states that "there is no question that every hour counts and that those receiving intraspinal or intravenous injections within the first few hours of definite symptoms show a much greater percentage of recovery than those given in the table by Dr. Irons."

By far the largest series studied numbered 1458 cases reported from the British Army by Bruce.[28] These were cases in England and therefore had comparatively long incubation periods. This

final analysis is the summing up of several previous preliminary reports, through which opinions on various points were evolving. The mortality was 34.8 per cent.

Bruce emphasizes the difficulty in appraising the value of antitoxin once symptoms have begun. The fact that cases were treated in different ways, and that patients were suffering from other serious ills, such as wounds, fractures, septicemia, pneumonia, hemorrhage, etc., weakens the value of any tetanus mortality figures that may be obtained.

In spite of the teaching that if a lethal dose of toxin has been taken up by the nerves and is traveling toward the nervous centers before treatment is begun, no amount of antitoxin will save the patient, the British Tetanus Committee believe in giving the patient the benefit of the doubt and using large doses at the earliest possible moment by the intrathecal route.

They recommend at least 24,000 units in twenty-four hours. Twenty c.c. of high potency serum containing 16,000 units may easily be given intrathecally on the first and second day. This, if supplemented and continued by intramuscular and subcutaneous injections, should be sufficient.

They do not urge intravenous treatment because of the greater likelihood of producing anaphylactic shock.

Anterior Poliomyelitis

The basis of serum treatment in anterior poliomyelitis rests upon the observations of Römer and Joseph[29] that immune bodies are present in the blood of recovered cases. The experiments of Flexner and Lewis[30] showed that the intraspinous injection of an immune serum sometimes is effective in preventing experimental poliomyelitic infection in the monkey when intravenous injection does not.

Flexner and Amoss[31] showed that similar protection was afforded if the virus was injected intraspinously or intravenously.

Netter[32] was the first to treat human cases and reported some success in the treatment of cases of the acute ascending variety.

Sporadic reports occurred until 1917, when Nuzum and Willy[33] reported 157 cases treated intravenously and intraspinously, injecting a total quantity of from 40 to 75 c.c. of a serum produced by immunization of animals with the streptococci cultivated from poliomyelitic cases. Amoss and Eberson[34] tested Nuzum's serum and found that when applied to their method it failed to show

in the monkey neutralizing or therapeutic power against small doses of the virus of poliomyelitis. Under the same conditions the serum of monkeys recovered from experimental poliomyelitis proved neutralizing and protective.

Although Rosenow used his immune horse serum intravenously, it is interesting to note that Amoss and Eberson were unable to find any evidence that it possessed any effective therapeutic value in monkeys, or possessed the antibodies of the same nature as those present in the blood of monkeys which have recovered from experimental poliomyelitis.

Immune sera have been used by Amoss and Chesney,[35] Zingher,[36] and Le Boutillier,[37] who decided that immune sera were of some value.

Peabody[38] is inclined to believe no good case can be made out for serum in anterior poliomyelitis.

Epidemic Encephalitis

In 1918 Netter[39] recommended intraspinal injections of convalescent sera, with which he had seen good results in anterior poliomyelitis. He now feels that the long duration of the disease appears to render this treatment futile.

The most serious attempt at treatment has been made by Rosenow, who grew a peculiar streptococcus isolated from the tonsils, teeth and nasopharynx of patients suffering from various forms of encephalitis. The serum of immunized rabbits and horses has been used by him in a number of cases and favorable results in one-half of the cases reported. The injections were made intramuscularly, intravenously and intraspinally. In a number of cases in which improvement was noted, the agglutinating titer of the patient's serum against encephalitic strains showed, twenty-four hours after the serum was given, a sharper increase than would be accounted for by the amount of serum injected. It is possible, therefore, according to Rosenow, that some of the good effects are non-specific in character.

The specificity of the organism has not been accepted and the therapeutic results of Rosenow have not been substantiated.

Various Meningitic Conditions

A few cases of recovered pneumococcic meningitis have been treated by pneumococcic serum by Cumming,[40] and Lamar.[41]

Cases of influenzal meningitis rarely recover, and of thirteen recoveries one had been treated by convalescent serum intraspinally, and one by autogenous and stock vaccine intraspinally. Neal[42] is interested in intraspinal treatment by vaccines, and mentions one case of staphylococcic, one of influenzal and one of Bacilli coli meningitis.

Bacigalupo[43] has reported two recoveries in three cases of tuberculous meningitis treated by intraspinal injections of tuberculin.

Non-Specific Sera

As a result of their experiments regarding the antibactericidal properties of human serum, MacKenzie and Martin,[44] in 1908, injected from 15 to 20 c.c. of fresh human serum into the spinal canal of 16 patients with meningococcic meningitis. Ten of these patients recovered. Since then a relatively large number of cases has been treated by autoserum injections. On the whole, the use of human serum has not been followed by brilliant results.

Pneumococcic meningitis has been treated by injections of antimeningococcic serum. Stainforth[45] and Hollis and Pardee[46] refer to the case of tuberculous meningitis treated by Schaeffer in 1913, by the intraspinal injection of antimeningococcic serum, and report recovery of 2 undoubted and 2 doubtful cases following this treatment.

Streptococcic meningitis has been treated by McCarthy[47] with normal horse serum.

Following the report of Goodman,[48] Langley Porter[49] treated 7 cases of chorea by intraspinal injections of normal horse serum with some improvement, but with no cures or with as striking results as Goodman's.

Further experiences with autoserum are reported by Brown, Smith and Phillips,[50] who are favorably impressed with this method.

Epidemic encephalitis was treated by Brill[51] by intraspinal injections of autoserum, and by Fendel[52] with an influenzal serum.

Drugs

Sicard,[53] in his thesis, refers to the intraspinal injections of non-toxic solutions, sodium chloride in dementia paralytica, potassium iodide in cerebrospinal syphilis, and potassium bromide in epilepsy, all without result. In 1902 Seager[54] recommended

lysol in the treatment of meningococcic meningitis. Manges[55] tested its effect upon a number of patients. Wolff[56] recommended protargol following the recovery of 5 out of 8 patients whom he treated. Coglievina[57] used dispargin, a colloidal silver preparation, in a case of epidemic meningitis and in a case of streptococcic meningitis, both of which recovered. He quotes 2 cases of epidemic meningitis, one treated by Villard and one by Gandean, with electrargol. Rocaz[58] used colloidal tin in a case of staphylococcic meningitis. Optochin (ethyl hydrocuprein hydrochloride), a cinchona derivative, has been employed in experimental septic meningitis by Kolmer[59] and clinically in epidemic and septic meningitis by Friedemann,[60] and Kolmer.[61] Vucin (isoctyl hydrocuprein dihydrochloride), another cinchona derivative, has been employed in septic meningitis. This drug is reported to have a germicidal value four times as great as that of optochin and no greater toxicity for the human body. Lewy[62] analyzed 12 cases treated by Linck, Zimmerman and Kurt Huenges. Six of the 10 cases reported by Linck recovered, but in only one was there a positive culture, in this case a staphylococcus. Lewy reported 7 cases. All of the patients who showed a positive culture from the spinal fluid eventually died. Only one of his patients recovered.

Unfortunately, the use of drugs in the treatment of meningitis is without avail. Flexner and Amoss[63] tested the bactericidal power of a given strength of lysol and protargol both in vivo and in vitro, and found them to be without effect. They concluded that "the chemicals have shown themselves not to be curative but rather to be injurious."

In 1906 Meltzer and Auer[64] called attention to the possible value of magnesium sulphate as an adjunct in the treatment of tetanus. They recommended injections of 25 per cent aqueous solution, giving 1 c.c. per 10 kg. of body weight. Meltzer thought that death occurred as the result of severe and exhausting spasms which could be controlled by magnesium sulphate. This procedure is attended by a real danger of paralyzing the respiratory center and stopping the heart. Robertson[65] has presented a careful study of the merits of this treatment. He collected 81 cases, all of which has received magnesium sulphate in addition to other treatment. The mortality was 44.4 per cent. He found the subcutaneous method of injection distinctly safer and concluded that "there can be no doubt in the minds of those who review the evidence that in magnesium sulphate we possess a most valuable addition to

our armamentarium in the treatment of tetanus." However, Bruce,[66] in his final report of the British series, says that magnesium sulphate in the Home Hospitals proved a failure.

It may be mentioned that Leonard[67] reported favorably upon the use of intraspinal injections of magnesium sulphate in 12 cases of delirium tremens.

A few isolated reports may be found on the treatment of other diseases, as adrenalin in anterior poliomyelitis, by Lewis.[68]

Irrigations

Horsley[69] treated a single moribund case of meningitis with spinal subarachnoid irrigations of a weak bichloride solution without result. Since that time a number of others have performed irrigations with normal salt solution and solutions of antiseptics, usually without result. Formachidis[70] has recently reported the successful treatment of a case of epidemic meningitis by irrigations of the spinal cavity with normal salt. Weed and Wegeforth[71] have shown that the chemical irritation, even of normal salt solution, is so great that death followed from respiratory failure in a high percentage of experimental animals. In another series of animals with experimental meningitis Wegeforth and Essick[72] irrigated the spinal canal with many of the commonly used antiseptics and found that none prolonged life.

Spinal Puncture

The majority of the cases of recovered influenzal meningitis reported by Neal and of pneumococcic meningitis reported by Lamar were treated by lumbar punctures alone. Royster[73] reported 2 additional cases of pneumococcic meningitis. In other cases of meningitis reported by Kuemmell, Netter and Tedesco,[74] and also by Bourges[75] the treatment consisted of repeated lumbar punctures. Because of unsatisfactory sera in use in England during the early months of the war, some authorities stated that the old method of lumbar puncture was the better form of treatment for epidemic meningitis. Foster and Gaskell[76] especially recommended lumbar puncture. Olitsky,[77] in an epidemic in southern China in 1918, had the opportunity of seeing cases which received no treatment and those in which lumbar punctures alone had been performed. The mortality rate without treatment in 104 cases was 84.6 per cent; with repeated lumbar punctures in 346 cases it was 54.1 per cent.

In view of the unsatisfactory reports from others, one is inclined to believe that the diminution in deaths may have been due to other reasons.

Following the observation of Steinebach,[78] that the course of delirium tremens was shorter and milder following lumbar puncture, the procedure has been employed in a number of cases. Hoppe[79] believes that lumbar puncture offers a valuable aid in the treatment of acute alcoholism and delirium tremens.

Occasionally lumbar puncture has been used in the treatment of status epilepticus and in the convulsions of eclampsia and uremia (Wilson[80]).

Lumbar puncture is of undoubted, if but temporary, value in diabetes insipidus resulting from hypothalamic lesions. A case of Herrick's,[81] of four years' duration, was reported in 1912 in which polyuria and polydipsia disappeared after lumbar puncture, to recur three years later. A similar result was obtained in a case of Graham's.[82] Tucker[83] reported a case with disappearance of the polyuria and quoted the case of Cammidge. Hall[84] quoted 3 cases of Maranon and Gutierriz, all beneficially affected.

Lumbar puncture as a means of relieving increased intracranial tension following injuries to the head, especially those without skull fracture, has been widely recognized and was practised in the late war (Leriche[85]). Albert[86] concluded that it was the only efficient treatment for basal skull fracture and for concussion. Jackson[87] called attention to its efficacy in preventing the sequelae of head injuries ordinarily grouped under the term "traumatic neurosis."

Continuous Drainage

This procedure is more properly a surgical subject. Dandy[90] recently reviewed the literature and called attention to a small number of cures of various types of purulent meningitis and proposed a modification of the Haynes operation. He reported four cases of streptococcic and staphylococcic meningitis treated by cisternal drainage, with three cures and one death.

Among miscellaneous procedures may be mentioned injections of air or oxygen into the cerebral ventricles and subarachnoid space. Sharp[88] reported three recoveries among 12 cases of tuberculous meningitis, the diagnosis not being verified by bacteriological findings.

Treatment by lumbar puncture and subcutaneous injection of the patient's spinal fluid has been employed in the treatment of epidemic encephalitis by Regett.[89] Unfortunately, his favorable results have not been generally repeated.

The Distribution of Dyes Introduced Subdurally

Admitting the possibility of subdural treatment of diseases of the central nervous system, certain requirements must be met for its successful consummation. It is necessary to have a drug, serum or other agent which has a specific action of a desired character, an innocuous action on nervous tissue, and a method for its introduction so that it may be brought into contact with all parts of the central nervous system in a required concentration and adequate amount.

That the latter requirements have not been attained may easily be seen from the long and often illogical controversies between those who favor intravenous and those who favor intraspinal methods of treatment of syphilis of the central nervous system.

Many investigations have been made of intravital staining of the central nervous system, in which it has been pointed out that certain dye stuffs are distributed only over parts of the central nervous system following their endolumbar introduction. It is unnecessary for our purpose to discuss the question of whether the nervous tissue is or is not actually intravitally stained by such methods.

Dandy[90] in his recent contribution on meningitis stated that if a cubic centimeter of India ink replaces an equal amount of cerebrospinal fluid in the cisterna magna, the ink granules will be freely distributed throughout the most distant branches of the subarachnoid space (over the cerebral hemispheres) in less than one hour.

If the cerebrospinal fluid and its contents did not disappear, by whatever mechanism, absorption, diffusion or osmosis, no further search would be necessary for a proper route for subdural treatment. Unfortunately, as pointed out by Halliburton[91] and others, diffusible substances introduced into the subarachnoid space pass rapidly into the veins. Especially rapid is the diffusion of liquid in the subcerebellar region. Dercum[92] alluded to this fact as of great importance in pointing out the apparent fallacy of treating syphilis of the central nervous system solely by intraspinal methods.

Whatever dyes various workers may have used, they are all agreed that meninges covering only certain parts of the brain are stained heavily by endolumbar injection. Goldmann,[93] who was particularly concerned with the study of the impermeability of the central nervous system to dyes introduced intravenously, was able to stain only the base of the brain, the cerebellum, the olfactory lobes, the optic nerves, brain stem and spinal cord by endolumbar injection. Following him, MacCurdy,[94] although not admitting the actual intravital staining of the brain, found approximately the same distribution of the dye. Woolsey[95] found, following sublethal doses introduced subdurally, that the meninges in some areas were not more stained than by intravenous injection. One of us (L.J.P.[96]) corroborated the former results of the gross distribution of dyes. It was found that unless injected with lethal force or in excessive quantities, solutions of dyes introduced by the endolumbar route did not stain the cerebral hemispheres or the meninges covering them to any degree. When an injection was made subdurally over a hemisphere, the stain reached the meninges covering it, the brain stem and cerebellum, but was very faintly and irregularly distributed over the opposite hemisphere and the spinal cord.

We wish again to point out that for the purpose of treatment we are not concerned with the eventual destination of small quantities of dyes or drugs, but with the rapid circulation of solutions of sufficient concentration, and the avoidance of dilution and absorption which occur as time elapses.

The most important communication relating to this subject is that of Solomon, Thompson and Pfeiffer[97] who experimented with injections of neutral phenolsulphonephthalein in the lumbar subarachnoid space, the cisterna magna and the lateral ventricles. They pointed out that fluid introduced into one of these regions could be drawn to another region by aspiration. Solomon stated that when a lesion was cerebral the site of election for injection was the subarachnoid space of the brain, or the ventricles. The experiments suggest that the displacement of the dye in the subarachnoid spaces is the result of diffusion and not of a true spinal fluid circulation.

When a solution of dye or drug is introduced into the subdural space, it is analogous to the introduction of a certain quantity of fluid into a closed vessel practically full of liquid. If an Ehrlenmeyer flask be filled with water, corked and inverted, and 5 c.c.

of water removed through a glass tube penetrating the cork, and 5 c.c. of a solution of methylene blue introduced, the stain will remain in the neck of the flask for a long time and complete diffusion will not have occurred even at the end of two hours. If now, while the dye is being introduced through a glass tube corresponding in a rough way to the spinal canal, water be permitted to flow out of the flask through an opening roughly corresponding to the position of the basal subarachnoid spaces, the dye will circulate freely into the lower part of the flask, then diffuse slowly through-

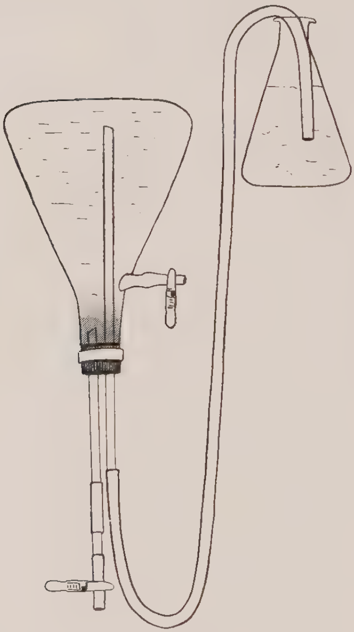

FIG. 70. Distribution of dye injected into closed vessel nearly full of water.

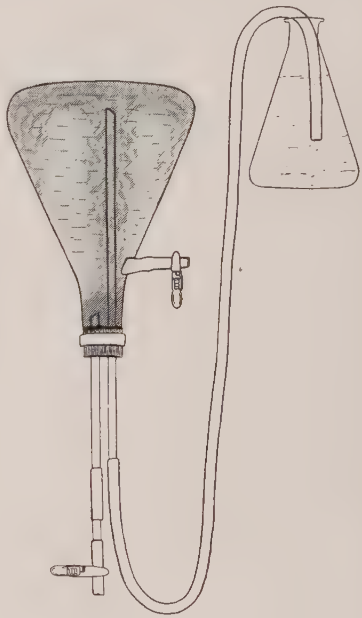

FIG. 71. Distribution of dye injected into closed vessel while water escapes from upper level.

out the remainder. If the rate of injection is greater than the outflow, only a small quantity can be introduced and this will not diffuse much higher into the flask than in the first experiment. If a second glass tube be introduced through the cork, extending to the upper level of the fluid in the flask, and water be permitted to escape from it while the dye is introduced through the first glass tube corresponding to the spinal canal, the dye very rapidly rises to the upper level of the fluid in the flask and quickly and thor-

oughly mixes with it. It may be seen that the diffusion of the dye is hastened by currents in the fluid into which it is introduced, and that the injection of the dye into a space almost filled with liquid does not result in rapid diffusion, because no active circulation of the fluid is produced. This we believe is, in a rough way, analogous to the conditions attending subdural injections into the cerebrospinal fluid. When injected by lumbar puncture alone, the

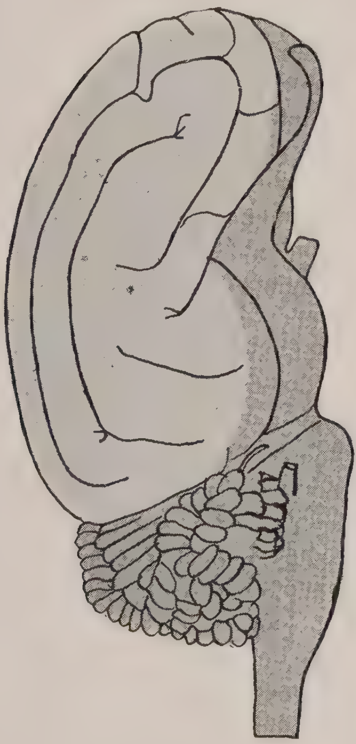

FIG. 72.

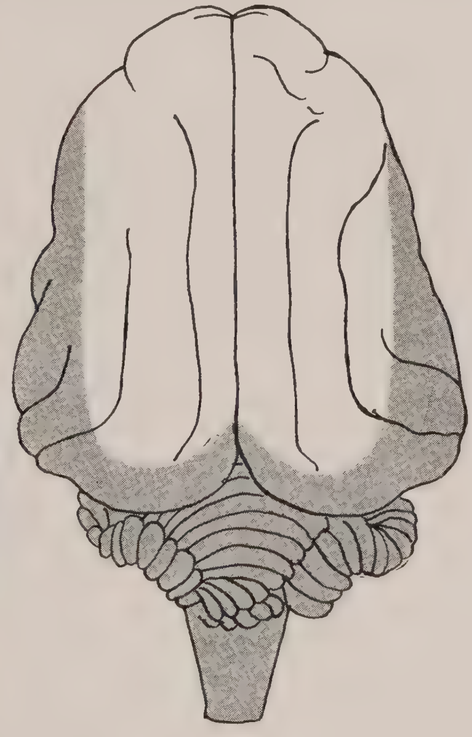

FIG. 73.

FIGS. 72 and 73. Distribution of stain over brain of cat when injected through lumbar puncture.

drug or dye enters a space filled with an incompressible fluid and tissue compressible only to a slight degree. For this reason, circulatory currents are not produced by the injection.

We found, as before, that the injection of solutions of methylene blue by lumbar puncture alone failed to stain the cerebral hemispheres or their coverings except at the base. The cerebellum was freely stained, as was the brain stem. If the dye was introduced

by cisterna magna puncture, the cerebellar fossae contained a greater amount of stain than before, the brain stem was more deeply colored, as was the base of the brain, but the convexity of the hemispheres remained unstained. By injecting the dye subdurally over one of the hemispheres, we were able to stain freely that hemisphere and its coverings. The cerebellum showed a greater amount of stain immediately adjacent to the tentorium, the base

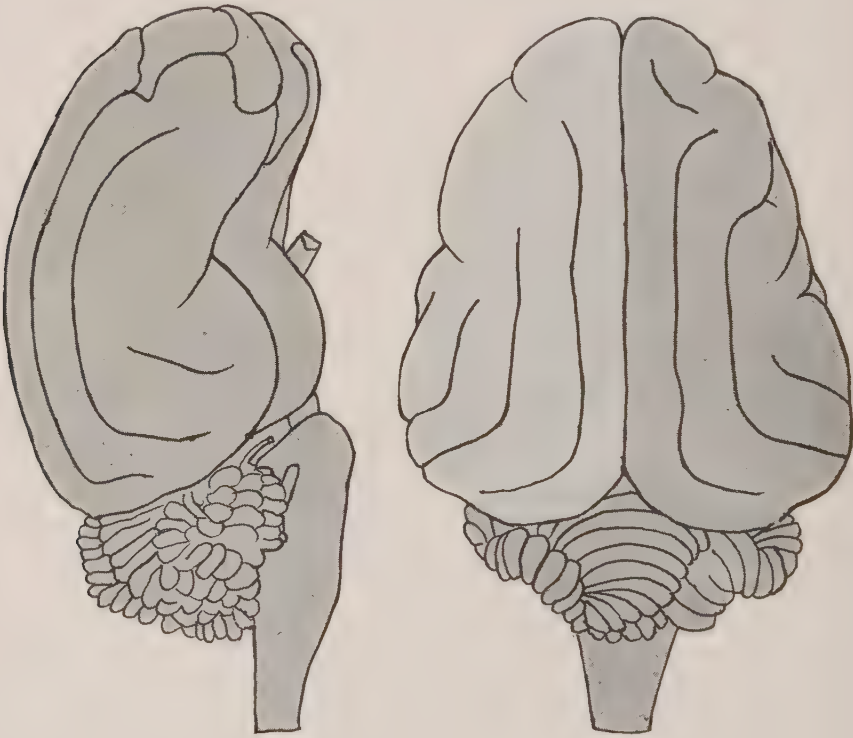

FIG. 74. FIG. 75.

FIGS. 74 and 75. Distribution of stain over brain of cat when injected through lumbar puncture, while the cerebrospinal fluid escapes from puncture of dura over a hemisphere.

was well stained, but the opposite cerebral hemisphere and its coverings showed very little stain.

Allowing the cerebrospinal fluid to escape from an opening in the dura over one hemisphere, while the dye was being introduced by lumbar puncture, permitted the rapid distribution of the dye *to all parts of the central nervous system.* It may be said that the opposite cerebral hemisphere was not as deeply stained, but the

dye was found in large quantities. By this means a quantity of dye may be introduced without the lethal effect which would result from increased intracranial tension if intraspinal injection alone were practised. It is well to refer to a former experiment in which it was found that, when a subdural injection of a dye was made over a cerebral hemisphere and the fluid permitted to escape from a lumbar puncture, the opposite cerebral hemisphere was unstained, indicating that artificial circulation of cerebrospinal fluid is not produced as readily in this direction.

We propose that the only efficient method for reaching the hemispheres by subdural injection is to create an artificial circulation of the fluid by permitting it to escape through an opening in the dura over a hemisphere while an injection is being made into the lumbar subdural space or cisterna magna; that intraspinal, cisternal or cerebral subdural injections alone are inefficient.

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Chapter XXXI

INTRASPINAL TREATMENT IN SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

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AS an introduction to the main part of this chapter, the following résumé of the evolution of intraspinal therapy in neurosyphilis is offered:

The evolution of present-day subarachnoid or intraspinal therapy in neurosyphilis had its origin in the well-controlled work of Swift and Ellis[1] which was published July 13, 1912. They reported not only the results obtained by subarachnoid injection of human serum following intravenous salvarsan in man, but included their observations of the effect on monkeys of intraspinal injection of monkey serum to which salvarsan and neosalvarsan had been added in vitro. They recommended the use of inactivated serum salvarsanized in vivo as efficacious but advised against the direct method of adding salvarsan or neosalvarsan to serum in vitro because it produced symptoms of cord irritation. Two weeks later, August 1, 1912, Wechselmann[2] reported the successful subarachnoid injection of neosalvarsan in two adults and two infants with neurosyphilis. He did not, however, draw any conclusions as to its efficacy either clinically or serologically.

Preceding the preliminary report of Swift and Ellis, Camus[3] and Marinesco[4] mentioned the subarachnoid use of salvarsan. The former in December, 1910, condemned the intrathecal injection of salvarsan because all dogs receiving such injections died, even with such small amounts as 0.0005 gm. of salvarsan per kilogram of weight. Marinesco, in January, 1911, after discussing the treatment of syphilis, casually mentioned having treated two patients with salvarsanized human serum by the subarachnoid route. Not having been impressed by the response to this type of treatment, he did not continue his investigation.

Soon after the articles by Swift and Ellis and Wechselmann, Castelli[5] reported the subarachnoid injection of neosalvarsan in ten dogs without harmful effects and Colleville[6] reported the intraspinal injection in two patients of 10 c.c. of serum to which 2 mgms. of salvarsan were added. In the following year Marinesco[7] reiterated his opposition to intraspinal therapy after unfavorable results in thirteen patients treated by Wechselmann's method. At this time Ravaut,[8] in the attempt to overcome the unfavorable sequelae following intraspinal therapy, recommended the use of a hypertonic neosalvarsan solution. He dissolved 0.6 gm. of the drug in 10 c.c. of sterile water, making a 6 per cent solution, one drop of which contained 3 mgms. of neosalvarsan.

From 1 to 4 drops, or 3 to 12 mgms., were added in vitro to the cerebrospinal fluid and injected intraspinally. A year later von Schubert[9] and Gennerich[10] also advised intraspinal injections of neosalvarsan, 1 to 3 mgms. dissolved in cerebrospinal fluid in vitro. In the same year Byrnes[11] reported the intraspinal injection of mercurialized autogenous serum. To 12 c.c. of serum he added 1 c.c. of a solution of mercuric chloride in freshly distilled water, containing 0.0013 gm. or $\frac{1}{50}$ of a grain of the drug, and heated the mixture for one-half hour at 56°c. He reported negative serological findings in 37 per cent of the thirty-two patients treated and a clinical improvement similar to that following the intraspinal method of Swift and Ellis. Ogilvie,[12] desiring to inject a known amount of salvarsan, added from $\frac{1}{4}$ to 4 mgms. of a neutral solution of salvarsan to the salvarsanized serum of Swift and Ellis or non-salvarsanized autogenous or heterogenous serum and inactivated at 56°c. for one-half hour.

It might not be amiss at this point to draw upon the experimental data which sanction the intraspinal injection of salvarsanized serum. Swift and Ellis[13] early studied the action of the serum of rabbits and serum of syphilitic patients treated intravenously with salvarsan and neosalvarsan upon the Spirochaeta duttoni. They found that such serum was spirocheticidal both in vitro and biologically when injected into susceptible animals, and also that the spirocheticidal action is increased by heating the serum for one-half hour at 56° c. (Cerebrospinal fluid is not inactivated, as it does not contain the inhibitory substance present in normal unheated serum.) They proved conclusively the efficacy of heated autogenous serum of untreated syphilitics by reducing several strongly positive cerebrospinal fluids to normal in all phases by the subarachnoid injection of this inactivated serum without any concomitant treatment for syphilis.

In their clinical work Swift and Ellis[14] found that in 60 to 80 per cent of cases of various types of neurosyphilis they obtained a complete clinical and serological arrest, some of their cases having been under observation for ten years without a relapse. Ogilvie,[15] using his modification of their method, claimed complete clinical remission in 34 per cent of 34 patients with dementia paralytica. Cotton[16] noted an arrest in 35 per cent of 31 patients and Stoner[17] observed a complete clinical and serological arrest in 20 per cent of 72 patients treated for over four years according to the Ogilvie modification. Cummer and Dexter[18] reported good clinical and serological response in 13, or 72 per cent, of tabetics and in 6 patients (100 per cent) with syphilitic meningitis. Thomas[19] recorded 25 cases of neurosyphilis, with 12 per cent clinically cured and 28 per cent greatly improved. Goldfader[20] found 64 per cent of 42 patients improved. Keidel and Moore[21] reported that 60 per cent of 25 patients showed good clinical results. Schaller and Mehrtens[22] noted clinical improvement and serological arrest in 64 per cent of 75 patients. Wittgenstein[23] recorded serological arrest in 42 per cent of 40 patients. Stokes and Shaffer,[24] in a recent report of 405 cases of neurosyphilis under observation from three and one-half to seven years, noted good to excellent results, which means practical return to symptomatic and serological normality, in 90 per cent of patients with meningeal neurosyphilis; in 74.5 per cent of patients with cerebrospinal neurosyphilis; in 48.3 per cent of patients with tabetic neurosyphilis, and in 38.9 per cent of patients with vascular neurosyphilis. Two-thirds of these patients received intraspinal therapy according to the Ogilvie modifica-

tion of the Swift-Ellis method in connection with intravenous salvarsan and sodium iodide and intramuscular mercuric succinamid. Marthens,[25] in April, 1924, reported very favorably upon the intraspinal use of pooled arsphenaminized fortified serum. Solomon,[26] in September, 1924, stated as his opinion that the Swift-Ellis method of intraspinal therapy is the most satisfactory and is indicated in many cases of neurosyphilis which have not otherwise been successfully treated.

Draper,[27] in January, 1925, reported his observations on a series of cerebrospinal syphilitics treated by intravenous and intraspinal therapy ten years before.[23] Nine patients whom he was able to follow up were found to have remained symptom-free and negative serologically during this period of time.

Gennerich,[29] the enthusiastic advocate of intraspinal therapy on the Continent, has, since the fall of 1921, employed the so-called double puncture, method. He inserts two needles, one or two interspaces apart, to which are attached two burettes or containers. Eight or 10 c.c. of cerebrospinal fluid are drawn off for serological tests, then 20 c.c. are collected in the upper burette and the burette is clamped. The spinal fluid is then allowed to collect in the lower burette until the spinal canal is virtually drained. In women 40 to 60 c.c. and in men 60 to 80 or 100 c.c. may be withdrawn. To the 20 c.c. of cerebrospinal fluid in the upper burette, freshly prepared neosalvarsan is added in a dosage of 0.5 to 4 and even to 5 mgms. The mixture is gently agitated so as to distribute the neosalvarsan evenly and is allowed to run slowly into the canal. Following this the spinal fliud in the lower container is permitted to flow back and thus wash the salvarsanized fluid toward the base of the brain. The patient is placed in bed for three or four days with the foot elevated twelve inches.

The objection to this form of treatment is the incidence of symptoms of cord irritation, such as difficulty in emptying the bladder, numbness of the anoperineal region, bladder and rectal incontinence and even complete paralysis of the lower extremities. Another objection to its use is the three or four day rest in bed which this method entails.

In a recent article Gennerich[30] claims that in endolumbar treatment by his method, mortality as a result of convulsions or other reactions is less than 0.1 per cent and that the frequency of spinal cord irritation does not amount to more than 0.5 per cent. Optic atrophy, he states, has been checked in every case in his series.

Before the introduction of the modern arsenicals in the treatment of syphilis of the central nervous system and the correlation of laboratory findings in the spinal fluid with its various clinical manifestations, our therapeutic methods were effective only in controlling the more obtrusive symptoms. In the great majority of cases relapses occurred with a decreasing therapeutic response. We are now able to visualize in a more or less accurate manner the relationship of the earlier implantation of the spirochetes to the later types of the infection and to measure and control by our serological tests the effects of specific drugs. Therapeutic and prognostic indications are derived from a careful study of the clin-

ical and laboratory findings in all types of neurosyphilis. Clinicians who treat syphilis of the central nervous system meet cases which are resistant to the usual systemic methods or which improve to a certain point and then remain stationary. A new method of therapeutic approach in these types is clearly indicated.

It is becoming more and more generally recognized that syphilis of the central nervous system begins during the early dissemination of the spirochete when foci are established which may at a later period cause pathological conditions to which various names have been applied. Early neurosyphilis is more frequently seen by the specialist in the disease or by the general practitioner, and late neurosyphilis by the neurologist or the internist. A correct conception of the relation of one phase to the other can only be obtained by cooperative work and careful clinical and laboratory control over a period of years.

If the assumption is true that the late types develop from the earlier ones, the importance of early adequate treatment as a prophylactic measure is self-evident. Furthermore, since our observations have shown that certain of these earlier infections are asymptomatic and revealed only by spinal fluid examinations, the necessity of such investigations for diagnosis and as a criterion of cure has become more generally recognized. In other words, the physician who undertakes the treatment of a recent syphilitic infection should visualize its possibilities and have sufficient knowledge of neurological signs and symptoms to recognize its early beginning in the central nervous system, and should insist on a lumbar puncture in all cases before a final pronouncement of cure. The prophylaxis of many late types is theoretically possible if all early cases are properly treated and controlled. The illogical assumption that early neurosyphilis is cured by the treatment usually employed and that a later infection occurs has very little to uphold it except vague clinical impressions. It is not supported by our knowledge of the pathology of the early infection through the lymph and blood streams or by the observations of clinicians who follow the infection from its inception. Fournier long ago showed that the greatest incidence of neurosyphilis was in the first two years and that it gradually diminished after that time. Students are often misled by textbook statements as to the time after infection when paresis and tabes are met with. These statements take cognizance chiefly of the fully developed clinical types

and disregard the long period of latency or overlook the obscure symptoms which such patients may present.

It is a well-established fact in the treatment of syphilis that the sooner it is begun, the quicker and more permanent is the response. After the introduction of salvarsan the incidence of neurosyphilis was noted more frequently than after the older methods of cure. Our knowledge of early neurosyphilis in fact has been largely developed since 1910 by systematic spinal fluid examinations in the endeavor to elucidate the pathological conditions which caused the various cranial nerve affections so frequently seen after subcurative treatment as then employed. We were taught by the the older syphilographers to delay treatment until the secondary rash appeared in order to be sure of a correct diagnosis. The disease, at this time uninfluenced by drugs, probably called forth an antibody response which affected not only the peripheral but the central nervous system infection. Salvarsan, as at first used, quickly influenced the visible manifestations and suppressed the formation of antibodies. The nervous system infection, deprived of this protection, proceeded with greater intensity than was the case under the older methods. In other words, a temporary sterilization of the peripheral affection was found to be possible by a few doses of salvarsan with a loss of antibody control of the infection in its more inaccessible location. Further experience with the new agent, however, taught us the value of repeated doses and its combination with mercury as the most efficient method of combating the disease in its various phases and localities.

Treatment during the first two years of the infection should be carried out regardless of the Wassermann reaction in the blood. If symptoms pointing to involvement of the central nervous system develop during the early period, a spinal fluid examination is imperative. If these symptoms persist during the administration of drugs by the systemic route, intraspinal treatment should be instituted and persisted in until all the findings in the fluid become negative. Statistics show that it is possible to cure by intraspinal treatment practically all cases of early neurosyphilis. While at this stage the infection usually involves the meninges, autopsies show that in some cases the blood vessels of the piarachnoid are involved to a considerable depth in the cerebral tissues. It is quite likely in these cases that a deeper deposition of spirochetes also takes place, and it may be necessary to persist in treatment over a period of one to three years, as illustrated in the following case:

Early Syphilitic Meningoencephalitis

D. (aged 36), in February, 1913, had a chancre on index finger followed by secondaries. Treatment included 12 injections of salvarsan, 46 mercury salicylate injections, 25 injections of gray oil and mixed treatment over a period of several months. The Wassermann reaction gave negative results on several occasions, but returned to positive on cessation of treatment. The patient was apprehensive and nervous most of the time. For a year he failed to come under observation. When seen again in May, 1916, nervousness and excitability were noted. The pupils were slightly unequal and irregular, but reacted promptly to light and accommodation. All deep reflexes were hyperactive, those on the left side more markedly so.

Table XLVII

Findings in a Case of Early Syphilitic Meningoencephalitis

Date	Cells	Cerebrospinal fluid		Gold sol	Blood Wassermann	
		Globulin	Wassermann			
6/ 3/16	172	3+	4+ 0.2 c.c.	5555430000	2/20/13	++++
6/24/16	116	4+	4+ 0.2 c.c.	....	6/ 2/13	–
7/21/16	45	3+	4+ 0.4 c.c.	....	2/21/14	++
8/26/16	10	3+	4+ 0.4 c.c.	5555420000	11/20/14	–
10/ 7/16	8	2+	4+ 0.6 c.c.	....	2/24/15	++
11/18/16	12	2+	4+ 0.6 c.c.	5554420000	6/19/15	–
12/ 9/16	9	2+	4+ 0.6 c.c.	....	9/29/15	++
1/ 6/17	7	2+	4+ 0.6 c.c.	....	12/15/15	–
2/10/17	10	2+	4+ 0.6 c.c.	5555432000	5/20/16	+++
3/31/17	9	2+	4+ 0.6 c.c.	....	8/26/16	–
4/30/17	6	2+	3+ 0.6 c.c.	....	10/28/16	–
6/19/17	0	1+	3+ 0.8 c.c.	5555442100	4/28/17	–
7/ 7/17	5	1+	4+ 1.0 c.c.	....	1/12/18	–
8/ 3/17	3	±	2+ 1.0 c.c.	....	2/12/19	–
10/ 6/17	3	±	4+ 1.5 c.c.	5555421000	2/21/20	–
9/11/18	2	±	4+ 2.0 c.c.	2223100000	1/21/21	–
1/11/19	3	±	4+ 2.0 c.c.	....	1/14/22	–
2/12/19	1	trace	– 2.0 c.c.	1233210000	3/ 2/23	–
3/21/19	0	trace	2+ 2.0 c.c.			
5/10/19	2	trace	– 2.0 c.c.			
6/ 5/20	2	trace	– 2.0 c.c.			
1/19/22	2	trace	– 2.0 c.c.	0000000000		

Treatment from June 8, 1916, to June 12, 1919:

4 intravenous injections of salvarsan. This treatment had to be discontinued owing to severe reactions.

45 intraspinal injections (Swift-Ellis, fortified with 1/10 to 8/10 mgm.).

12 injections of mercury; several courses of potassium iodide and mixed treatment.

Results. The patient has remained in good health; he is free from nervousness and is able to continue his work without undue effort. In January, 1922, his heart was found to be enlarged, with an accentuated and roughened aortic second sound and a systolic murmur over the base. His blood pressure was 178/110; on June 15, 1922 it was 210/130; on March 2, 1923, 200/110. He has had no symptoms which are referable to the cardiovascular condition.

The treatment of neurosyphilis should be based on a clear conception of its pathology. In the one type treatment may be effective because the specific drugs are brought into direct contact with the organisms; in the other it fails because the organisms cannot be reached, no matter in what manner the remedies are introduced. It is well to keep in mind, however, that transitional forms exist which give the clinical and laboratory findings of paresis, but which respond to prolonged treatment. A paretic formula in the spinal fluid, uninfluenced by prolonged treatment, indicates a potential paresis even in the absence of the usual clinical signs or symptoms (see Case H, page 506).

In early syphilitic meningitis which may follow the vessels into the superficial parts of the brain parenchyma, a paretic curve is frequently met with, but under treatment, this rapidly changes to the luetic curve and then to normal as shown in the following case:

Early Syphilitic Meningitis

S. (aged 45). The initial lesion in April, 1916, was not followed by cutaneous secondaries. The Wassermann test was ++++. Treatment from April to August 1916 comprised 7 intravenous injections of salvarsan and 16 injections of mercury. Treatment was interrupted because of the patient's absence from the city. In October, 1916, the patient became nervous and restless and had mild generalized headaches and nausea. Transient attacks of aphasia and numbness of right arm were noted for several days. On returning to New York on October 28, examination of the patient showed weakness of the right side of face, very active deep reflexes, which were more marked on right side, and slightly irregular pupils with prompt light reflexes.

Treatment from November 1, 1916 to May 19, 1917:

6 intravenous injections salvarsan.

11 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with ⅕ to ½ mgm.).

18 injections of mercury.

TABLE XLVIII

FINDINGS IN A CASE OF EARLY SYPHILITIC MENINGITIS

Date	Cells	Cerebrospinal fluid		Gold sol	Blood Wassermann
		Glob-ulin	Wassermann		
10/31/16	944	4+	4+ 0.2 c.c.	5555542100	5/ 6/16 ++++
11/24/16	90	4+	4+ 0.4 c.c.	4444430000	6/14/16 ++
12/ 6/16	31	3+	4+ 0.6 c.c.	....	8/12/16 –
12/16/16	30	2+	4+ 0.8 c.c.	....	10/31/16 ++++
12/30/16	30	3+	4+ 1.0 c.c.	1133320000	3/ 3/17 –
1/12/17	50	2+	4+ 1.0 c.c.	1123310000	9/ 6/17 –
1/27/17	28	2+	4+ 1.0 c.c.	1123210000	1/12/18 –
2/10/17	20	1+	4+ 1.0 c.c.		
3/ 3/17	21	±	± 1.0 c.c.	1123100000	
3/24/17	18	±	1+ 1.5 c.c.		
4/14/17	8	±	– 2.0 c.c.	1112210000	
5/19/17	8	trace	– 2.0 c.c.	0000000000	

Results. Patient resumed his occupation in February, 1917, at which time he was feeling very well and energetic. His headaches and numbness disappeared after the second intraspinal injection. He suffered no further attacks of aphasia. He was employed by the Government for two years during the World War and was able to attend to his duties without difficulty. Up to May, 1923, he showed no further developments of the disease.

Does Arsenic Given Intravenously Penetrate to the Central Nervous System, and What are the Factors Involved in Intraspinal Therapy?

In order to understand better the physiology and chemotherapy of the various arsenicals employed in the treatment of syphilis, we have conducted during the past four years a series of investigations[31] for the purpose of determining the localization of these antisyphilitic remedies in the various tissues and fluids of the body and to study the metabolic processes which take place after their administration.

Briefly, after a study of thousands of specimens, we have found that arsenic leaves the blood stream very rapidly after the completion of the injection, except in a few instances where idiosyncrasies prevail. After salvarsan injection 60 per cent of the drug is localized outside of the blood stream; after neosalvarsan, 62.1 per cent; after

silver salvarsan, 56.4 per cent; and after tryparsamide, 64.1 per cent is found outside the blood stream.

To ascertain the relative amount of arsenic in the serum and clot, separate determinations[32] were made. These analyses have showed that the clot possesses a maximum capacity for holding arsenic where proper separation is carried out and that the serum obtained after the intravenous injection of neosalvarsan contains about five times as much arsenic as serum obtained after the intravenous use of the other drugs. From the point of view of the Swift-Ellis method of treatment, therefore, serum after neosalvarsan is preferable to any of the others unless fortification is to be employed, in which case salvarsan should be used.

The literature dealing with the penetration of arsenic into the spinal fluid and the central nervous system has been somewhat vague in the past, some authorities believing that arsenic did not penetrate, while others claimed that it did, but with great difficulty. To study this question of penetrability several hundred spinal fluids were analyzed. These investigations[33,34] distinctly pointed out that arsenic at some time during a course of treatment penetrates into the cerebrospinal fluid. It further emphasized the point that it is not so much the quantity of arsenic as the quality which is desired; that is, whether it is active or inactive arsenic. Response to treatment, however, depends on additional factors such as the site of organisms, type of lesion, etc., as in the patient cited below:

TABES

J. K., aged 28. Chancre in 1910; secondaries denied. Had local treatment only at time of infection. Between 1914 and 1915 received 32 injections of salvarsan; no mercury. Came for advice because his Wassermann reaction remained positive. Complained of occasional twinges of pain in his extremities.

Physical Examination. Pupils were unequal, fundi normal; vision, 20/20 both eyes. His reflexes in the upper extremities were equal and active. One knee jerk and both ankle jerks were absent; other findings negative.

Serology.	Blood,	9/13/17	+
		12/29/22	++++
	Cerebrospinal fluid,	9/13/17	Cells 7
			Glob. ++++
			Wassermann ++++ to 0.4
			Gold Sol: luetic curve
		12/29/22	Cells 5
			Glob. ++
			Wassermann ++++ with 0.6
			Gold Sol: paretic curve

Results. Under prolonged treatment his blood was negative for nearly two years. It then became and remained positive. His spinal fluid by May 3, 1919, was reduced to ++ with 1.5 c.c. It remained positive with this amount until March, 1922. He was urged to take six months' rest from all therapy, but instead went to a private physician and had 18 injections of neosalvarsan. When he returned in October, 1922, his fluid was positive with 0.6 c.c. and gave a paretic curve. It next showed ++++ with 0.2 c.c. and continued so, with a paretic curve, until the last examination on April 5, 1923. It was noted during the previous months that he became very irritable at times. Beyond this and an extreme apprehensiveness regarding his condition and reluctance to follow advice relative to rest from treatment, no mental abnormalities were noted. On April 28 he complained of feeling ill and after a few days went to a hospital where a diagnosis of typhoid fever was made. He died on May 12, 1923.

TABLE XLIX

TREATMENT AND ARSENIC DETERMINATIONS IN A CASE OF TABES

Previous no. intravenous injections	Previous no. intraspinal injections	Salvarsan dose, gm.	Interval after intravenous injections, hours	Arsenic per 100 gms., dried specimen, in mgms.
78	40	0.4	48	5.13
79	41	0.4	48	0
80	42	0.4	48	trace
81	43	0.4	48	0
82	44	0.4	48	4.13
84	46	0.4	48	21.2
85	47	0.4	48	2.10
86	48	0.4	48	1.15
87	49	0.4	48	4.41
96	50	0.4	48	13.5
97	51	0.4	48	3.08

Remarks. The first examination showing 5.13 mgms. of metallic arsenic was made 48 hours after an intravenous injection following a four months' rest from all treatment. The next four treatments were taken two weeks apart, then a month elapsed before the examination showing 21.2 mgms. The succeeding three treatments were two weeks apart. The cerebrospinal fluid showing 13.5 mgms. was taken eight months after the last intraspinal injection, he having received, however, in the meantime eighteen intravenous injections of neosalvarsan from an outside physician.

Our clinical studies have shown that the presence of arsenic even in large amounts is not necessarily accompanied by a concomitant improvement either in symptoms, as, for instance, in general paresis, or in the serology. We are obliged, therefore, to invoke

other factors to account for the benefit that follows intraspinal therapy. It has been shown by the experiments of Swift and Ellis,[35] and later by Eberson,[36] that the serum from old syphilitic cases contains some spirocheticidal substances. It is not illogical, therefore, to assume that the arsenic, plus antibody, plus the mechanical removal of the cerebrospinal fluid and hyperemia of the meninges are the factors involved in bringing about amelioration or cure of neurosyphilis.

Which Is the Therapeutic Method of Choice?

The original Swift-Ellis method is the one we have consistently employed over a period of more than twelve years, except during the intervals when other methods were tried out, such as that of Ogilvie with the reinforced serum, or the addition of neosalvarsan direct to the cerebrospinal fluid as advocated by Ravaut and employed by Gennerich, or the Byrnes method of mercurialized serum. All of these procedures were discarded because of the irritation produced in the lower portions of the spinal cord.

We have, as a result of our clinical experience and arsenic investigations, made the following observations:

1. The best bleeding time is one-half hour after an intravenous injection and the drug of choice is neosalvarsan. Analyses of blood made at intervals varying from five to sixty minutes after salvarsan, silver salvarsan and neosalvarsan injection showed that between the intervals of twenty to sixty minutes a uniformly higher value was found for neosalvarsan than after the other two drugs and that the optimum time was thirty minutes. With blood taken at shorter intervals, say fifteen to twenty minutes, the risk of an excess of arsenic followed by symptoms of irritation of the cauda equina is present.

2. The serum should remain in contact with the clot overnight. The day following treatment the blood should be centrifugalized, the serum pipetted off and centrifugalized again to insure absolute clarity.

3. The serum should be inactivated for one-half hour at 55° to to 57°c.

4. At the time of administration of the salvarsanized serum, at least 30 c.c. of cerebrospinal fluid should be permitted to run into the receptacle. The serum is added and the mixture permitted to flow into the subarachnoid space by elevating the gravity tube.

In this way the possibility of irritation is lessened. The amount of fluid removed depends on the pressure at the time of treatment.

What Are the Indications for Intraspinal Therapy?

1. All cases of neurosyphilis with definite findings in the cerebrospinal fluid which are not responding to treatment intravenously and in which advanced degenerative changes in the lower cord are not present call for intraspinal therapy.

2. Cases which have become intolerant to salvarsan intravenously, as evidenced by exfoliative dermatitis, jaundice, etc., need intraspinal therapy. We have found by experience that if the arsenicals are prepared with a 0.4 per cent sodium chloride solution, properly diluted and administered by the gravity method, a better distribution of the arsenic in the body fluids is obtained and the chances of an exfoliating dermatitis and jaundice lessened.

3. In optic atrophy where the initial process is presumably due to a basilar meningitis it is possible to arrest the progress of the atrophy by continued intraspinal treatment. We have observed a number of cases which had received large amounts of arsphenamine intravenously in which an examination of the spinal fluid showed all phases positive, with a cell count of from 20 to 182.

What Are the By-Effects Which Follow Intraspinal Therapy?

Reactions after intraspinal treatment closely simulate those which occur at times after intravenous injections; that is, the tabetic pains become intensified and bladder, gastric or other crises may become more frequent. After each succeeding treatment, however, these symptoms lessen and finally disappear, and we have come to look upon them as rather favorable signs indicating the specific action of the drug on the lesions in the central nervous system. These so-called reactions which are allied to the Herxheimer reaction are less apt to occur in individuals who have received a certain amount of systemic treatment before the employment of intraspinal injections.

In syphilis of the brain reactions after either the intravenous or the intraspinal injection may at times assume such a menacing character as to imperil the life of the patient. It is difficult to make a differential diagnosis of cases of the so-called Herxheimer reaction due to the rapid effect of the drug on the specific lesions, or hemor-

rhagic encephalitis due to the drug itself. Both of these conditions may manifest themselves by convulsions, rise of temperature and prolonged coma. Hemorrhagic encephalitis usually results in death; the Herxheimer reaction offers a better prognosis. Patients have been observed to recover from repeated convulsions and coma after forty-eight hours and to show a very marked improvement in their previous symptoms.

Within twenty-four hours, or later, after an intraspinal treatment by some of the modifications of the original Swift-Ellis method, patients may develop numbness of the genital organs, slow bladder with retention of urine, anesthesia of the buttocks, inability to control the bowels, weakness in the lower extremities and in some cases a total paraplegia. Even with the Swift-Ellis method, if the blood is drawn fifteen minutes after injection, at which time it contains a relatively large amount of arsenic, or if the intervals are too short, minor symptoms referable to irritation of the cauda equina may result. If the blood is taken thirty minutes after administration of arsphenamine, and intraspinal injections are not given at shorter intervals than two weeks or, as a rule, three weeks, these by-effects are not produced.

How Long Can Patients Tolerate Intraspinal Therapy?

The tolerance to intraspinal treatment depends on the type of involvement of the central nervous system. Tabetics are most sensitive and symptoms of cord irritation are apt to develop, especially in those with a low involvement. Patients with certain indefinite forms of so-called meningovascular neurosyphilis, and paretics, tolerate treatment over years with little or no reaction. This is well illustrated in the following history:

PARESIS

H. (aged 38). In 1904 this patient had an initial lesion with a secondary rash and mucous patches, for which he took treatment by mouth until 1910. At this time he developed a left external palsy and suffered from shooting pains in the legs with cramps in his calves. When examined in December, 1912, his deep reflexes were very active, especially on the right side. He had no sensory changes. Station, gait and coordination normal. Pupils equal and regular, light reflex sluggish on right side. No mental symptoms. Lumbar puncture refused for one year.

TABLE L

FINDINGS IN A CASE OF PARESIS

Date	Cells	Cerebrospinal fluid		Gold sol	Blood Wassermann
		Globulin	Wassermann		
12/12/13	26	2+	4+ to 0.2	....	12/20/12 ±
6/ 9/14	10	2+	4+ to 0.4	....	6/ 9/14 ±
9/ 9/14	8	2+	4+ at 0.4	....	9/10/15 ±
10/21/14	3	2+	4+ to 0.4	....	1/12/16 —
12/21/14	38	2+	4+ to 0.4	5555555420	3/14/17 —
1/15/15	30	2+	4+ to 0.4	....	3/ 6/18 —
4/ 6/15	0	2+	4+ to 0.4	5555555420	1/15/19 —
5/21/15	1	2+	4+ to 0.4	....	10/10/20 —
7/ 8/15	12	2+	4+ to 0.2	5555555420	3/15/22 —
9/10/15	4	2+	4+ to 0.2		
10/ 9/15	0	4+	4+ to 0.2		
3/29/16	11	3+	4+ to 0.4	5555555420	
4/26/16	9	3+	4+ to 0.4		
6/ 3/16	8	3+	4+ to 0.4		
7/ 8/16	12	2+	4+ to 0.4		
9/13/16	10	2+	4+ to 0.4		
10/24/16	19	3+	4+ to 0.4	5555555530	
12/20/16	18	3+	4+ to 0.4		
1/31/17	11	3+	4+ to 0.2		
3/14/17	12	4+	4+ to 0.2	5555555530	
4/25/17	9	3+	4+ to 0.2		
6/16/17	5	4+	4+ at 0.4		
10/ 3/17	38	4+	4+ to 0.4	5555555410	
11/21/17	3	4+	4+ to 0.4		
7/24/18	6	2+	4+ to 0.4	5555555420	
8/22/18	4	2+	4+ to 0.4		
9/18/18	7	2+	4+ to 0.4		
10/30/18	14	4+	4+ to 0.2		
12/ 4/18	9	4+	4+ to 0.2	5555543100	
1/15/19	5	3+	4+ to 0.2		
10/10/20	4	2+	4+ to 0.2	5555543100	
2/12/21	6	2+	4+ to 0.2		
3/15/22	5	1+	4+ to 0.2	5555554210	

Treatment. From January 6, 1913 to March 15, 1922:

59 intravenous injections of salvarsan.

72 intraspinal injections of salvarsanized serum, numerous courses of mercury injections, with potassium iodide and mixed treatment. (During 1912 the patient received 3 injections of salvarsan intramuscularly and 4 injections intravenously.)

Results. Except for occasional pains in his legs, patient felt entirely well mentally and physically until early in 1922. He never lost a day from his work as stationary engineer except when he had treatment. In March, 1922, he became nervous and apprenhensive about his condition; toward the end of the month he suddenly developed convulsions. Following these he was disoriented, excitable and so unmanageable that he was placed in an institution where he remained until his death on July 10, 1922.

What Are the Contraindications for Intraspinal Therapy?

1. Neurosyphilis with a negative cerebrospinal fluid.

2. Cases which are being favorably influenced by intravenous treatment.

3. Markedly alcoholic subjects.

4. The aged with sclerotic changes.

5. Low tabes with advanced degeneration.

6. Cases which do not tolerate the treatment, as evidenced by severe headaches, meningism, or where symptoms of irritation of the lower portion of the spinal cord have developed.

Results Following the Use of the Intraspinal Method

In making a detailed analysis, about eighteen months ago, of 443 cases of neurosyphilis which had been observed in my private work over a period of ten years, the following classification, based on clinical and laboratory findings, was made:

Secondary neurosyphilis, i.e., of the meningeal, meningovascular and meningoencephalitic types, occurring within the first two years of the disease, 19 cases.

Tertiary neurosyphilis, i.e., after the second year of the infection, including vascular and meningovascular types, tabes imperfecta and well-developed tabes, general paresis and optic atrophy, 424 cases.

The 19 secondary neurosyphilitics who had received from one to three courses of previous intravenous treatments complained of such symptoms as headache, insomnia, vertigo, aphasia, facial palsy, tinnitus and impaired hearing. All had a positive Wassermann reaction in the blood and a positive spinal fluid. In nine the cell count ranged from 25 to 944 and in ten it was under 25. In seventeen patients the Wassermann reactions were strongly positive in the high dilutions; seven gave a paretic curve and ten a luetic one. From one to five courses of combined intravenous and intraspinal treatment were given. In one instance where it was impossible to administer the arsenicals intravenously because of

an extreme sensitization, forty-five intraspinal injections were given before a cure was obtained. Eighteen cases of this secondary group which have been followed up have been symptom-free and negative serologically for periods varying from one and one-half to seven and one-half years.

EARLY SYPHILITIC MENINGITIS

L. (aged 32). Surgeon. Chancre of thumb in 1916 with secondary rash. Two months later, while under treatment, complained of headache localized to right parietal region. Spinal fluid in May, 1917, was reported to show 104 lymphocytes, with the other phases weakly positive. After three intraspinal injections the fluid was said to be normal. Headaches still continued and increased in intensity a few months later, with insomnia, depression and mental impairment and marked loss in weight. He was seen on November 20, 1917. On the 26th he became very excitable and developed a delirium lasting several days.

TABLE LI

FINDINGS IN A CASE OF EARLY SYPHILITIC MENINGITIS

Date	Cells	Cerebrospinal fluid: Globulin	Cerebrospinal fluid: Wassermann	Gold sol	Blood Wassermann
11/28/17	416	3+	4+ 0.4 c.c.	1123321000	11/28/17 —
12/ 8/17	43	1+	4+ 0.6 c.c.	1123221000	2/ 9/18 —
12/22/17	11	1+	3+ 0.8 c.c.	....	3/25/19 —
1/ 5/18	7	±	4+ 1.5 c.c.	....	9/12/24 —
1/19/18	2	±	— 2.0 c.c.	0000000000	
1/30/18	0	±	— 2.0 c.c.		
2/ 9/18	1	—	— 2.0 c.c.	0000000000	
3/29/19	2	—	— 2.0 c.c.	0000000000	
9/12/24	2	—	— 2.0 c.c.	0000000000	

Treatment from November 23, 1917 to February 9, 1918:

8 intravenous injections salvarsan.

7 intraspinal injections salvarsanized serum (Swift-Ellis, fortified with 1/5 to 1/4 mgm.).

Results. After three intravenous and two intraspinal injections the patient's mental condition entirely cleared and his headaches disappeared. He continued to improve rapidly and became entirely well mentally and physically and has been able to look after a large practice since. From time to time the foregoing treatment has been supplemented by courses of mercury intramuscularly, together with mixed treatment.

Dr. X. (aged 30). Nose and throat specialist, who infected both index fingers while performing a tonsillectomy in April, 1919. In the latter part of the same month, treatment was begun and he received 13 injections of arsphenamine, 48 of bichloride of mercury (gr. $\frac{1}{10}$) and potassium iodide, up to 60 grains, three times daily for twelve weeks. In spite of this he developed intense temporal headache and projectile vomiting in the latter part of September. Then four injections of arsphenamine were given and 10 mercurial rubs, with an occasional treatment of each up to January, 1920. An iridocyclitis appeared at this time. Four injections of arsphenamine relieved the pain and congestion. In March, 1920, when he came under observation he had no vision on the temporal side of the left eye. The neurological and general physical examinations were negative. A summary of treatment and serological findings follows:

TABLE LII

FINDINGS IN A CASE OF EARLY SYPHILITIC MENINGITIS

Date	Cells	Cerebrospinal fluid		Gold sol	Blood Wassermann
		Globulin	Wassermann		
3/27/20	67	4+	4+ to 0.6	2332100000	4/10/20 ±
4/14/20	102	4+	4+ to 0.6	....	6/23/20 ±
5/ 5/20	15	1+	4+ to 0.6	1121100000	7/28/20 —
5/26/20	7	1+	4+ to 1.5		
6/23/20	4	±	3+ to 2.0	1110000000	
7/28/20	4	±	— to 2.0		
11/12/20	2	trace	— to 2.0	0000000000	

Treatment, from April 8 to November 12, 1920:
6 intravenous injections of arsphenamine.
6 intraspinal injections (Swift-Ellis).

Results. The eye remains unchanged, the ophthalmologist's report being that the floating exudate of the original iridocyclitis is the same in amount and opacity. The vision corrected with a 50-diopter lens has relieved the eye-strain headache. In addition to the above treatment the patient has continued his intravenous injections.

EARLY SYPHILITIC MENINGOENCEPHALITIS

J. B., male, colored, age 28. Chancre, November, 1919. Treatment was begun six weeks later with appearance of rash. After 8 salvarsan and 12 mercury injections he discontinued treatment for one month, then developed iritis, deafness and a week later right-sided facial palsy with left-sided palsy two days later. Was dizzy, unsteady and staggered. He received syphilitic treatment from his physician and prominent symptoms yielded rapidly.

Physical Examination. When seen two months later showed residua of facial paralysis; all deep reflexes were very active and greater on the left side.

Serology.	Blood,	3/24/20	++++
		7/28/20	−
	Spinal fluid,	3/24/20	Cells 210
			Glob. ++++
			Wass. ++++ to 0.4 c.c.
			Gold sol 5533211000
		5/27/22	Cells 3
			Glob. −
			Wass. − with 2.0 c.c.
			Gold sol 0000000000

Results. On his return to the Clinic on March 24, 1920, he was placed on further intravenous treatment combined with drainage. His cerebrospinal fluid became almost negative, but after the ninth drainage it relapsed and was stronger than it had been in the beginning, the cells having increased to 280. Intraspinal injections were then given and the fluid gradually returned to normal after 21 intravenous and 15 intraspinal injections.

TABLE LIII

TREATMENT AND ARSENIC DETERMINATIONS IN A CASE OF EARLY SYPHILITIC MENINGOENCEPHALITIS

Previous no. of intravenous injections	Previous no. intraspinal injections	Salvarsan, dose, gms.	Interval after intravenous injection, hours	Arsenic per 100 gms., dried specimen, in mgms.
17	9 Dr. * 3 S.E. †	0.4	48	6.9
18	9 Dr. 4 S.E.	0.4	24	4.7
19	9 Dr. 5 S.E.	0.4	48	0
21	9 Dr. 6 S.E.	0.4	48	1.5
23	9 Dr. 8 S.E.	0.4	48	trace
24	9 Dr. 9 S.E.	0.4	48	0.64

* Dermatological Research Salvarsan. † Swift-Ellis Method.

Remarks. Prior to the third intraspinal injection which showed the highest value, four weekly intravenous injections had been received. The intervals between the othei injections were two weeks, excepting before the sixth, when it was six weeks.

Of the 139 patients with tertiary vascular and meningovascular syphilis the majority had subjective or objective signs, or both, referable to the central nervous system; 25 gave a negative Wassermann reaction in the blood, and the diagnosis might easily have

been overlooked if a complete investigation had not been carried out. In 87 patients the cells in the cerebrospinal fluid ranged from 0 to 25; in 23, from 25 to 50 and in 29, from 50 to 2900 cells per cubic millimeter. The Wassermann reaction was strongly positive in 114, 28 showing a paretic curve and 86 a luetic curve. Of the 16 patients with a negative spinal fluid, eleven intravenous treatments only were given, and they became negative clinically and symptomatically; and 34 patients with a positive fluid treated by the combined method, with two to four or more courses, also became negative clinically as well as in the blood and spinal fluid, the duration of these observations being two and one-half to eleven and one-half years. Sixty-five patients, the majority of whom did not follow their treatment consistently, showed a marked clinical improvement, but did not attain a serological cure.

Of 156 patients with tabes, 50 in the early stage and 106 with the classical syndrome, the Wassermann reaction of the blood was positive in 70 per cent and positive in the cerebrospinal fluid in all excepting one case; 25 per cent gave a paretic and 75 per cent a luetic gold sol curve. The cell count varied from 0 to 350 per cubic millimeter. Of the 50 pre-tabetic cases, 19 had more than two courses of combined treatment; 13 of these became negative and 6 remained stationary. The negative cases have been under observation for from two and one-half to eight and one-half years. Of the 90 fully developed cases, 30 had two or more courses; of these, 17 have been negative for from two and one-half to eleven and one-half years, with no progress in their clinical symptoms. Better results in tabes follow the use of intraspinal medication when an active meningitis is present. It is of little practical importance to make a clinical differentiation between the so-called pseudo-tabes and genuine tabes.

Of 118 patients with general paresis, no cures can be reported, even where intensive treatment has been followed. Fifty-two cases received less than one course of treatment and 53 received from two to five or more. In 65 patients remissions were induced which lasted from a few months to several years; one patient remained in the pre-paretic stage for eleven years and another patient has had no relapse of his mental symptoms for six years.

PARESIS

G. (aged 45). A chancre on prepuce in 1901 was followed by generalized rash and mucous patches in the mouth. Mercury pills were taken for four and a half years. In July, 1918, the patient became excited, extremely nervous and

had frequent crying spells, followed by periods of depression. He became forgetful, repeating the same statement several times, and was unable to assume any responsibility. For three months there had been slowness in micturition. Married in 1918, he conceived a dislike for his wife a month later and attempted to obtain a divorce. Examination showed the pupils irregular, unequal and sluggish. All deep reflexes were very active, more so on the right side. The left abdominal reflex was absent, the cremasteric was sluggish, and speech and mental processes very slow. The patient's memory was poor. Blood pressure was 127/75, the aortic second sound being somewhat accentuated

TABLE LIV

FINDINGS IN A CASE OF PARESIS

Date	Cells	Cerebrospinal fluid		Gold sol	Blood Wassermann
		Globulin	Wassermann		
10/12/18	68	4+	4+ to 0.2	5555554310	10/ 9/18 +++
11/ 9/18	52	4+	4+ to 0.2	5555543100	12/27/19 +++
11/23/18	15	3+	4+ to 0.2	....	7/14/20 ++
12/ 7/18	5	4+	4+ to 0.2	5555555420	9/15/20 +++
3/12/19	3	2+	4+ to 0.2	....	3/15/22 +
10/29/19	3	1+	4+ to 0.2	5555543100	12/18/22 +
12/24/19	5	1+	4+ to 0.2	....	11/13/23 −
2/18/20	5	2+	4+ to 0.2	5555531000	7/17/24 −
7/14/20	3	±	4+ to 0.2		
9/11/20	4	1+	4+ to 0.2	5555431000	
11/ 5/21	3	1+	4+ to 0.4	5555431000	
12/16/22	8	1+	4+ to 0.4	5554100000	
11/13/23	5	±	2+ to 0.4	5433321000	
7/17/24	3	±	1+ to 0.4	5443321000	

Treatment from October 8, 1918 to July 17, 1924:
46 intravenous injections of salvarsan.
44 intraspinal injections (Swift-Ellis).
Several courses of mercury intramuscularly and mixed treatment.

Results. The remission has lasted six years. In this time he has directed a large business. Aside from occasional spells of forgetfulness, there is no abnormality, his wife reports.

Remissions occur most frequently in patients with the meningeal picture in the foreground and are coincident with a reduction in the cell count and control of the superficial lesions. The following case history is introduced to illustrate this point.

I. B. (aged 43). Primary and secondary lesions twenty years ago. Had taken mercury pills for three and one-half years. For fifteen years had severe shooting pains. Had been nervous, irritable and sexually weak. A month prior to first observation, suffered a complete breakdown with grandiose manifestations, believing himself to be very wealthy, becoming extravagant and buying many unnecessary things. He lost fifteen pounds in weight. A neurological examination showed unequal, irregular and rigid pupils. The deep reflexes of the upper extremities were more active on the right side. The right patellar reflex was present but the left was absent. Achilles jerks absent; slight Romberg; memory and judgment poor; no speech disturbance.

TABLE LV

FINDINGS IN A CASE OF PARESIS

Date	Cells	Cerebrospinal fluid		Gold sol	Blood Wassermann
		Globulin	Wassermann		
6/25/19	668	++++	++++ to 0.2	5555543100	6/25/19 ±
7/16/19	118	++++	++++ to 0.2	....	3/10/20 ±
7/26/19	14	++++	++++ to 0.2	....	3/12/21 +++
8/ 9/19	77	++++	++++ to 0.2	....	7/15/21 +++
8/19/19	12	++	++++ to 0.2		
8/29/19	8	++	++++ to 0.2	5555431000	
9/16/19	7	+	++++ to 0.2		
11/26/19	5	+++	++++ to 0.4	5555431000	
12/10/19	5	++	++++ to 0.4		
1/31/20	5	+	++++ to 0.4	5555531000	
3/16/21	6	+	++++ to 0.2	5555553210	
7/15/21	3	±	++++ to 0.2	5555553210	

Treatment from June 24, 1919 to September 15, 1921:
42 injections of salvarsan, neosalvarsan and silver salvarsan.
21 intraspinal injections.
Several courses of mercury and iodides.

Results. A remission was brought about; the delusions of grandeur and irritability disappeared. The patient became tractable and able to look after his affairs, but after a few months there were periods of depression marked by crying spells and great forgetfulness. Improvements and relapses alternated until January 29, 1921, when there were two violent convulsions followed by recurring attacks during the next ten months, when he died.

In optic atrophy it seems convincing, from experience in the past, that persistent intraspinal treatment, when indicated by a positive cerebrospinal fluid and begun sufficiently early, will preserve a useful amount of vision. Analysis of 33 cases showed

9 to be of the simple optic atrophy type, 17 of the tabetic and 7 of the paretic type. Twenty-seven of the patients had a positive Wassermann reaction in the blood and 32 showed a positive Wassermann reaction in the spinal fluid, with cell counts ranging from 0 to 180 per cubic millimeter. Eight had complete atrophy before treatment; 7 had complete atrophy in one eye and partial atrophy in the other; of these 2 progressed and 5 became stationary; 17 had incomplete atrophy of both eyes; 12 improved with arrest of the process; and in 5 a further reduction of the visual fields was noted before the process ceased to progress. These cases were controlled by well-known ophthalmologists and have now been observed for from three and one-half to six and one-half years.

At times patients are met with in whom treatment for various reasons has been discontinued before all the phases in the fluid have become negative. A number of these cases examined after a period of months or years have given a negative fluid. These favorable results occur chiefly where a gradual reduction in the intensity of the various reactions takes place. Similar observations have been made in patients with systemic syphilis whose blood reactions following treatment have been positive but after a prolonged rest period have become negative and remained so. In many patients the cerebrospinal fluid does not become negative after prolonged treatment, although there is a cessation of all clinical symptoms.The question of the continuation of treatment in these cases must be based on the general condition, age, elimination, etc. On the other hand, patients are observed where the fluid reactions become stronger and the clinical symptoms intensified, when too long an interval elapses between treatments, so that the only accurate guide is a periodic examination of the fluid. As a rule, however, it is safer to give too much rather than too little treatment and to delay discharging a patient until the modern criteria of cure have been met.

Summary

In the prophylaxis and treatment of neurosyphilis the following conclusions are to be emphasized:

1. Prolonged and systematic treatment of early syphilis.
2. Early recognition of nervous system involvement.
3. Continuation of treatment until the cerebrospinal fluid findings are negative.

4. The proper selection, preparation and employment of specific drugs.

5. The superiority of neosalvarsan in neurosyphilis in the Swift-Ellis method of treatment.

6. The Swift-Ellis method should be used only in cases where the cerebrospinal fluid findings indicate an active process which does not respond to systematic treatment. In optic atrophy treatment should not be delayed.

7. In all types of neurosyphilis treatment must be continued at times over a period of years before the cerebrospinal fluid becomes negative.

8. Results following its use are probably due to the arsenic content of the serum changed in vivo, plus syphilitic antibodies formed in the peripheral circulation. Irritation and resulting hyperemia of the nerve tissue with which it comes into contact may also be a factor.

Discussion

The following questions submitted to Dr. Fordyce before the Commission, together with the answers to them, are here reported verbatim.

Dr. Sachs: I should like to ask Dr. Fordyce whether his preference for the intraspinal injection of serum following a neosalvarsan injection applies to the use of neosalvarsan as such versus the old salvarsan, or is it only the question of serum after neosalvarsan that he prefers?

Dr. Fordyce: The point that I attempted to bring out was the special indication for neosalvarsan when serum is to be used by intraspinal injection. Neosalvarsan given in the proper dosage in our experience is just as effective as the old salvarsan so far as the clinical manifestations of syphilis and its influence on the Wassermann reaction are concerned.

Dr. Sachs: I think we are all highly pleased that Dr. Fordyce has brought the result of his investigations and of his studies before this body. I am particularly gratified to see that there is a very considerable approach between the viewpoints that he has advocated and the viewpoint for which I have been more or less responsible during these past years. After all, there is a difference between the investigator who approaches this subject from the point of view of the dermatologist and syphilographer and those of us who have approached it from the neurological point of view. The one great difference between us is this: The syphilographer seems to attach unusual and perhaps excessive importance to the serological findings.

From our own experience, not only my own but the experience of a great many neurologists, the serological change is not invariably or indeed as a usual thing in direct proportion either to the change in the condition of the patient or to the lack of change in him, and for that reason most of us will

probably feel that it would be just as well, if not even better, to be guided by the general improvement or the change in clinical symptoms rather than by the change in serological conditions.

There are any number of patients who show clinical improvement when there is practically no change in the serological conditions, and there are an equally large number of patients who show distinct changes from time to time in serological conditions in the number of cells per cubic millimeter, in the globulin content, in the Wassermann reaction, who do not show any corresponding change in clinical symptoms.

The idea that I can not accept is that we must push treatment until we get satisfactory changes in serological conditions. That view has led to an excessive amount of treatment, and I am perfectly frank to say that I have seen a number of patients who have been subjected to innumerable intraspinous treatments carried on over a long period of years, who have not been benefited, but, as I thought, even harmed by the excessive amount of treatment. It is a safer principle, on the whole, in treating these patients suffering from syphilis of the central nervous system, to be guided by either the change in clinical symptoms or by the stationary character of the symptoms, and either continue or modify or remit the treatment in accordance with the general condition of the patient. I feel that if we depend altogether upon serological conditions, we are very apt not to bear sufficiently in mind the general condition of the patient.

I shall ask Dr. oFrdyce, then, if he does not think that his viewpoint is similar to the viewpoint which he knows that I have favored, and whether he does not, in the first instance, after all, feel that the first measure to use in the treatment is the intravenous administration of arsenic? Does he not favor using the intraspinous treatment only in cases in which the intravenous treatment does not seem to be successful?

Then may I ask Dr. Fordyce whether he does not think that, after all, the ill effects of the intravenous treatment are not nearly so marked as some of the ill effects after intraspinous treatment? May I ask him how often this exfoliative dermatitis occurs after intravenous treatment? In my own experience I have never seen it, where I have used intravenous treatments over a long period of time.

In view of the statements made by Dr. Pollock, does not Dr. Fordyce think that the reason why intraspinous treatment is not effective in the cure, for instance, of general paresis, and in the cure of other purely cerebral conditions is because the arsenic contained in the serum injected into the lumbar sac really does not reach the foci of the spirochetes in the brain, as we know that they are situated, or apt to be located, in the substance of the cortex?

And then I would finally like to ask Dr. Fordyce whether by the intravenous treatment we are not getting just as much arsenic into the intervertebral canal as we would probably be able to introduce there for any period of time by direct injection?

Dr. Fordyce: In the first place, I believe that the viewpoint of Dr. Sachs and that of the advocates of intraspinal therapy are gradually coming together. I think we are both perhaps becoming a little more tolerant. Of course, common sense and experience and the interpretation of clinical symptoms mean as much to me as the laboratory findings; but if we combine our common sense, our

experience and our clinical knowledge with the laboratory findings, I think we get further than if we take one viewpoint alone—do you not think so, Dr. Sachs?

Dr. Sachs: I do. I agree to that, provided you will give due consideration to the clinical improvement or lack of improvement.

Dr. Fordyce: In systemic syphilis if we are guided only by disappearance of the clinical manifestations, or if we rely too exclusively on a clinical cure alone, we are almost certain to be confronted later with relapses. In the central nervous system the same rule holds good. Permanent results can only be achieved by a proper correlation of clinical observations with the laboratory findings. Harm has undoubtedly resulted in certain cases from an excessive amount of both intravenous and intraspinal treatment, but more serious results to the patient have followed the omission of intraspinal treatment in cases where intravenous treatment has failed. This statement applies especially to cases of optic atrophy, early meningitis and tabes dorsalis with positive cerebrospinal fluid findings.

The question of arsenic penetration, as well as the other inquiries of Dr. Sachs, have been covered in the body of the paper.

It is impossible to state off hand the percentage of cases of exfoliative dermatitis which follow the administration of the various arsenicals: with proper technique, perhaps not more than one or two per cent. It usually follows some technical error or failure to note a slight dermatitis.

Dr. Sachs: May I ask just one other question that I have not referred to before, since we would all like to benefit by Dr. Fordyce's experience in this matter? Personally, I am letting up a little even on intravenous treatments. I have been resorting to sulpharsphenamine injections in chronic cases. Is Dr. Fordyce willing to express any opinion as to the relative influence of the use of this drug either on primary or secondary syphilis?

Dr. Fordyce: Our experience shows that sulpharsphenamine is only about one-third as efficient as neoarsphenamine or the old arsphenamine. I recently had a patient at the City Hospital who developed a very severe type of early meningitis after she had had fourteen injections of sulpharsphenamine. I do not think that this preparation is to have a permanent place in the therapeutics of syphilis. The incidence of dermatitis and arsenical neuritis is much more frequent after sulpharsphenamine than after the older arsenicals.

Dr. Ayer: What experience has Dr. Fordyce had with serum administered elsewhere than into the lumbar sac in paresis and optic atrophy?

How many paretics have become clinically and serologically arrested?

Dr. Fordyce: In answering the first question, I would say that I have had no experience in paresis except with the ordinary intraspinal method of treatment.

In answering the second question, I would state that very few of our paretics become serologically negative. Occasionally, we can influence the Wassermann reaction in the blood. In paresis the great majority, perhaps 99 per cent, have a very strongly positive blood and spinal fluid. In very few cases are the findings in the fluid changed by treatment, excepting the cell count and the globulin content. Sometimes in the terminal stages of the degeneration, the Wassermann reaction may become negative. The clinical symptoms are present, of course, in a state of advanced development even with the negative findings.

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APPENDIX A

APPENDIX A

A SURVEY AND SUMMARY OF SPINAL FLUID EXAMINATIONS FROM NUMEROUS HOSPITALS IN THE METROPOLITAN DISTRICT; WITH RECOMMENDATIONS

JOSEPHINE B. NEAL, M.D.

A STUDY of the data on the examination of spinal fluids obtained from several of the leading hospitals in New York City has served to strengthen the conviction that I have long held; namely, that in the examination of spinal fluids many workers are in the habit of "counting the tens and skipping the hundreds," the tens being the cell count and the hundreds being the bacteriology and the chemistry.

All will agree without discussion, I think, that whenever a lumbar puncture is done the spinal fluid deserves a complete examination which should include, at least: cytology, bacteriology, by smear and culture, and chemistry—albumin, globulin and sugar. In certain cases a Wassermann test, colloidal gold reaction or animal inoculation may be indicated.

Too often, however, even in our best hospitals where the most painstaking and complete examination is made of urine and blood, the spinal fluid receives only a cell count in the counting chamber, with perhaps a very casual statement as regards the albumin or globulin and sugar. Even the bacteriology receives scant attention. A Wassermann or colloidal gold is frequently done and sometimes these are the only data recorded. Our experience in the meningitis division has convinced us that a direct cell count is often very inaccurate, as it not infrequently happens that a very few red cells are present in an apparently clear fluid and they are often counted as leucocytes by even a moderately experienced examiner. Since only a small amount of acetic acid can be used in doing these cell counts, it is extremely easy for any but the most experienced workers to mistake these for small mononuclears. Consider the error that will arise if only a small fraction of a cubic centimeter of

blood is present in twenty cubic centimeters of cerebrospinal fluid. Therefore, it is our custom always to check cell counts with the examination of the fixed and stained sediment of a centrifuged specimen.

It must be borne in mind that the examination of spinal fluids may be considered from two entirely different points of view: the routine examination which is necessary for aid in clinical diagnosis with the knowledge at hand in regard to the value of spinal fluid findings; and the examination that is made from the viewpoint of the research worker in the hope of extending that knowledge.

We must remember that in comparatively few laboratories throughout the country is there the equipment or personnel for carrying out elaborate quantitative studies of spinal fluids. It is obvious that unless quantitative work is done with extreme care and accuracy, the results are worse than useless. In the meningitis division, where more than 11,000 fluids have been examined in the last fourteen years, we have been using a very simple technique for a rough quantitative estimation of the albumin, globulin and sugar, which has proved quite satisfactory for clinical work. At present, a quantitative determination of the sugar is made. This method has been followed in a few other laboratories, especially by Dr. Regan in the Kingston Avenue Hospital, with satisfactory results. The exact details are given on page 526. It is enough to say that the chemicals and equipment are extremely simple, and the method can be quickly learned by any intelligent laboratory worker so that it can be used even in the smallest laboratories.

The information obtained by it is sufficiently accurate for ordinary clinical work. The small amount of albumin and globulin present in normal fluids is marked by us $\pm$, not 0, as I have often seen it stated in hospital reports, and increasing amounts are marked $+$, $++$, $+++$, etc. We must remember that with our present knowledge the exact amount of increase in the protein present in spinal fluid has no special diagnostic value. There is no point, for example, at which an increase indicates a tuberculous meningitis rather than an encephalitis or poliomyelitis.

The sugar present is marked $+++$ when normal, $+++$ prompt, when increased, $++$, $+$, etc., when decreased. Of course the quantitative examination of sugar is now comparatively simple and may be made in only moderately well-equipped laboratories. Even so, there are many small laboratories and hospitals in the

country where even this equipment is not found, and the estimation of the amount of sugar, using equal parts of Fehling's solution and spinal fluid, we have found checks up very well with the quantitative determination. The sugar determination is especially important since a sugar content below normal in a clear fluid indicates, in the vast majority of cases, a tuberculous meningitis. An increased sugar content is sometimes found in poliomyelitis and encephalitis.

To an audience of this kind it may seem trite, but in dealing with the average physician in general practice it is necessary to emphasize that the only instances in which the diagnosis is *absolutely* made by the examination of the spinal fluid are in those cases of meningitis in which the organism can be demonstrated.

A diagnosis of tuberculous meningitis can be made with a very high degree of certainty, even if the tubercle bacilli are not demonstrated, where there is an increase in the cells and in the protein content and a decrease in the sugar. Likewise, a diagnosis of a syphilitic involvement of the central nervous system can be quite definitely made or ruled out by the Wassermann reaction and the colloidal gold curve.

The necessity, therefore, for careful bacteriological examination both by smear and culture cannot be too strongly emphasized. Smears and cultures should be made from the sediment of centrifuged specimens. The smears from all hazy or cloudy fluids should always be stained by the Gram method. The cultures from all fluids should be made both aerobically and anaerobically and cultures should not be pronounced sterile until ten days to two weeks have elapsed.

When cultures are obtained they should be carefully studied to determine their exact nature, and only from the culture should a definite diagnosis be made. From the smear it is possible to express only a tentative opinion, except, of course, in the case of tuberculous meningitis.

Simple as is the method that we use in the meningitis division in examining spinal fluids, it is far more complete than the examination made at most of our best hospitals. It would be of inestimable value, I think, if this method or one equally easy of application were recommended by so authoritative a body as the Association for Research in Nervous and Mental Disease, for the routine examination of spinal fluids. In laboratories where the procedure

can be carried out, quantitative determination of protein and sugar should, of course, be substituted for the less exact estimation.

While the scope of the paper read at this meeting shows that much research work has been done in the examination of spinal fluids, there is still a vast field to be explored. English and American workers have not followed so energetically as might have been expected the trails blazed and carried so far by Anglada and Mestrezat as early as 1908 and 1912 in France.

Of course, the study of the cerebrospinal fluid involves certain difficulties not encountered, for example, in studying the blood. It would be easy to induce fifty healthy people to allow us to withdraw an ounce or two of blood, in order to study the constituents of normal blood. One would hardly ask a well person to submit to a lumbar puncture for the sake of studying the normal spinal fluid; hence the specimens that we obtain are usually from individuals with meningeal symptoms. Unless the pressure of the spinal fluid is increased, we hesitate about withdrawing more than a few cubic centimeters; therefore, the amount of fluid from the more nearly normal cases is too small for extensive investigative work. It is, therefore, not easy to determine the exact limits of the normal content of the various constituents. Until a large number of fluids from each of a large number of diseases have been carefully analyzed we shall be in danger of drawing wrong conclusions from insufficient data. An example that comes to my mind is the statement made three or four years ago, that increased sugar was diagnostic of encephalitis. Those who made the statement were unaware that the sugar in certain cases of poliomyelitis is also increased. Of course, to have the greatest value, spinal fluid and blood chemistry estimations should be made at the same time.

The many lines of study that are open in the examination of spinal fluids are apparent to you all. I greatly envy those who have at their disposal the means to follow them.

Methods of Examining Spinal Fluids

The following is the method used in examining spinal fluids by the meningitis division of the Research Laboratory of the Department of Health, City of New York:

The amount of fluid is stated and the appearance described.

Cytology. A direct cell count is made in clear or hazy fluids if they are received at the laboratory within a short time after withdrawal. Care is taken to mix the fluid thoroughly before the count is made. The counts are always checked by the examination of the stained sediment of a centrifuged sediment.

The specimen is centrifuged for at least an hour and then the sediment in the bottom of the tube is carefully scraped off and spread on the slide over an area somewhat smaller than a cover slip.

The examination of this stained and fixed sediment rules out the error which might arise from a few red blood cells being present and counted as leucocytes. It is often noted that a few red blood cells are present in fluids that are apparently clear. These red blood cells may easily be taken for mononuclears in the counting chamber, since the small amount of acetic acid that must be used in counting the cells in spinal fluids often does not dissolve the red blood cells.

Experience has shown that in the examination of these stained and fixed sediments a fluid with a cell count of ten or less will show not more than one cell to an average of five or six fields. If more cells than this are present the fluid may be safely regarded as containing more than the normal number of cells and the increase may be marked as slight, moderate, great or very great.

While this method of estimating the number of cells is far from exact, it gives a sufficiently accurate idea of the cytology for clinical work. Direct cell counts often fail to give the exact number of cells in the spinal fluid on account of the presence of red blood cells and on account of the fact that when collected in successive tubes there is often a considerable difference in the number of cells in the first and last tubes.

The percentage of mononuclears and polymorphonuclears is also made from the stained sediments.

In the case of cloudy fluids, unless a direct cell count can be done within a few minutes after the withdrawal of the fluid, it will be practically useless, as the cells sediment out quickly and tend to form clots which prevent their even redistribution through the fluid.

The cell count of cloudy fluids has very little bearing on diagnosis or prognosis.

Bacteriology. The smears from clear fluids are always stained by the Ziehl-Neelsen method. Hazy fluids are stained by both the Ziehl-Neelsen and the Gram methods, and cloudy fluids by the Gram method.

Cloudy fluids should be centrifuged fifteen minutes or more in order to obtain the greatest number of organisms for the smears and cultures.

The web in a clear spinal fluid may be teased out and stained by the Ziehl-Neelsen method. Since we examine the fluids as soon as they are received in the laboratory, we have come to depend more on the sediment than on the web for finding tubercle bacilli. Fluids in cases of suspected tuberculous meningitis are usually centrifuged for at least two hours.

It has been found that Gram-positive organisms often decolorize easily in the smears made from the spinal fluid. We are, therefore, careful to make only a tentative report on stained specimens and to await the growth of the culture for a definite diagnosis.

Cultures should be made aerobically and anaerobically. As a meningococcus is the organism most likely to be found in the spinal fluid, we use as a routine medium for the aerobic inoculations, chocolate veal agar p. H. 7.8. Cultures of all fluids are made on this and anaerobically on semi-solid media. In the case of cloudy fluids cultures are also made on plain agar, blood plates and veal broth. In this way a diagnosis can usually be made in twenty-four hours.

But it sometimes happens when the organisms are few, especially in the case of the meningococcus, that the growth does not appear until forty-eight or seventy-two hours have elapsed. The cultures once obtained are thoroughly studied before they are discarded. The inoculated media are kept from ten days to two weeks before they are discarded.

Chemistry. During the summer of 1916, facilities were at our disposal for making quite complete quantitative chemical studies of the spinal fluid. Except at that time we have been obliged to rely on the qualitative tests that will be described. We found that the results obtained by these tests check very well with the quantitative examination.

The albumin is tested by the nitric acid ring test. This is done by putting about 0.5 c.c. fuming nitric acid into an agglutination tube and carefully floating on the top, by means of a pipette, about the same amount of spinal fluid. In a normal spinal fluid there is a barely perceptible ring at the juncture of the two fluids. This is marked ±. Increasing amounts of albumin are marked +, +1, ++, etc., up to ++++ massive, depending on the width and density of the ring.

The globulin is tested by the Noguchi butyric acid test. To one part (about 2 c.c.) of spinal fluid add 2 parts of a 10 per cent solution of butyric acid in normal saline; boil; add one part or less of normal NaOH and boil again. Care must be taken not to add too much NaOH. It is better therefore to add it drop by drop. The reading should not be taken until after an hour has elapsed.

With a normal spinal fluid there is a faint opalescence; this is marked ± as with the albumin. When there is a formation of flocculi, the globulin is increased and is marked +, +1, etc., up to ++++ massive. The increase in albumin and globulin is usually the same, but the two tests serve as a check on each other.

Until within the last few months, the sugar present has been estimated by the reduction of Fehling's solution. Equal parts of spinal fluid and Fehling's solution, about 3 c.c. of each, are boiled in a test tube. The mixture is allowed to cool before readings are made. When the sugar is normal in amount, there is a red precipitate of copper covering the entire rounded bottom of the test tube. When the sugar is increased in amount, this precipitate forms immediately when the mixture is boiled. The reduction obtained by a normal sugar content is marked +++; when the content is apparently above normal, +++ prompt. Precipitation of copper less than normal is marked ++, +1, +, ± and −. For several months quantitative colorimetric measurements by the Folin-Wu method have been used in addition to the reduction of Fehling's. It has been found that the Fehling estimations have checked very well indeed with the quantitative determinations. We therefore feel that Fehling's estimations are reliable and may be depended upon when it is not possible to make quantitative determinations.

Guinea pigs are inoculated with fluids from suspected cases of tuberculous meningitis when the organisms cannot be demonstrated in the smear. Whenever there is any question of a syphilitic involvement, a Wassermann test is made on the spinal fluid. While we should be interested in the study of colloidal gold curves, the facilities for doing these have been at our disposal only at intervals.

Discussion

The following question submitted to Dr. Neal before the Commission, together with the answer to it, is here reported verbatim.

Dr. Tilney: I should like to ask Dr. Neal what percentage of spinal fluid examinations seems to her satisfactory in the hospitals of the city of New York.

Dr. Neal: The percentage was very small. There were one or two outstanding examples of most excellent examinations. The work done at Bellevue Hospital, for instance, by Dr. John Little, was excellent, and the work done in some of the other hospitals was extremely good. The work done in the Neurological Department at Bellevue was very good, but I know in some of the other divisions the work is not done with that degree of care. I happen to see the reports collected from those divisions.

I should think that in not more than 10 per cent at most of the cases was there an examination made that was at all complete. In many instances there would be only a single factor recorded: either a cell count or a Wassermann or colloidal gold, and when the globulin or albumin was recorded, it was frequently recorded as either zero (which we know is not so; there is always a certain amount of albumin or globulin present in spinal fluid) or in some instances it was recorded as plus, with no attempt made to indicate whether there was marked increase or a slight increase. The same condition was present with regard to the sugar: the sugar was frequently put down as zero.

The conclusion that Dr. Regan and I make will be based largely on the results obtained at Dr. Regan's laboratory in the Kingston Avenue Hospital and at the laboratory of the meningitis division at the Research Laboratory. In both these laboratories complete examinations of the spinal fluid are made, although we have not been able to do so much quantitative work as we would have liked. The number of spinal fluids examined in these two laboratories, more than 2000 in Dr. Regan's laboratory and adding 11,000 in mine, is so large that it will be necessary to include only the findings from hospitals where complete examinations have been made.

APPENDIX B

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